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APPLICATION NUMBER: 60/493,447
FILING DATE: *August 08, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/25026*

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PROVISIONAL PATENT APPLICATION

Attorney Docket No. 22247-10600

TRANSMITTAL

Date: August 8, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a request for filing a Provisional Application for Patent under 37 C.F.R. 1.53(c).

1. INVENTOR(S)

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☐ Additional inventors are being named on the _____ separately numbered sheet(s) attached hereto.

2. Title:

COMPOUNDS AND COMPOSITIONS THAT MODULATE
METABOLISM, THEIR USE AND RELATED METHODS

3. Enclosed Application Parts

a. 223 pages of specification (including claims)

4. Method of Payment of Fees

☒ Applicant claims small entity status. See 37 C.F.R. 1.27.

☒ A check is enclosed to cover the filing fees. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 18-1260. A duplicate copy of this document is enclosed.

☐ The calculated fees are to be charged to Deposit Account No. 18-1260. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to said Deposit Account. A duplicate copy of this document is enclosed.

5. The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

16235 U.S. PTO
60/493447
08/08/03

Date: August 8, 2003

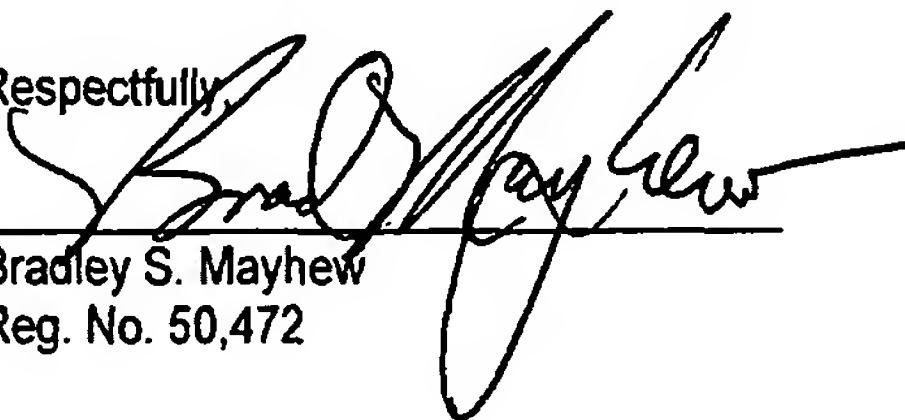
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Respectfully,



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**COMPOUNDS AND COMPOSITIONS THAT MODULATE
METABOLISM, THEIR USE AND RELATED METHODS**

The present application relates to the following previously filed applications, the entireties of which are herein incorporated by reference: PCT/US01/07527 filed on March 8, 2001; PCT/US02/07199, filed March 8, 2002; and U.S. Provisional Appl. No 60/408,887, filed September 9, 2002.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to compounds and compositions that modulate one or more of various metabolic activities. In particular applications, the invention relates to compounds and compositions that activate AMPK and/or Akt. In particular applications, the invention relates to compounds and compositions having blood glucose lowering activity and/or lipid lowering activity as well as to related methods. In particular applications, the invention relates to an anti-diabetic agent, to an anti-diabetic composition containing the anti-diabetic agent, and to a method for treating diabetes. In other particular applications, the invention relates to methods for screening purine derivatives and/or pyrimidine derivatives to identify compounds having an activity to modulate one or more of various metabolic activities and/or for use as an anti-diabetic agent.

Description of Related Art

2 Elevated blood glucose and blood lipids are a relatively common underlying
condition in numerous metabolic diseases and may be acquired in various ways. Among
4 other causes, elevated blood glucose levels are frequently precipitated by an altered
metabolism associated with a diabetic disease state.

6 The diabetic disease state is characterized by an impaired glucose metabolism that
commonly manifests itself in elevated glucose levels in patients suffering therefrom.

8 Generally, diabetes is classified into two distinct subgroups:

10 (1) Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), which arises
when patients lack β -cells producing insulin in their pancreatic glands, and

12 (2) Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which
occurs in patients with, *inter alia*, impaired β -cell function and/or impaired insulin
14 sensitivity (insulin resistance).

16 At present, type 2 diabetic patients are primarily treated with hypoglycemic agents
such as sulfonylureas that stimulate β -cell function and/or with agents that enhance tissue
18 sensitivity to insulin. Unfortunately, in many instances such treatment is not completely
satisfactory. For example, many patients gradually lose the ability to respond to treatment
20 with sulfonylureas and are thus gradually forced into insulin treatment. Moreover, various
adverse effects, including liver toxicity, have been associated with agents prescribed to
22 enhance tissue sensitivity to insulin.

 Where existing treatments prove ineffective in normalizing blood sugar levels of
24 patients, there is an increased risk of acquiring diabetic complications. For this reason,
discovering and identifying compounds for use in therapeutic approaches to achieve
26 satisfactory glycemic control has become an intensive area of research.

Particularly active areas of investigation have included searches for purine
2 derivatives and pyrimidine derivatives having hypoglycemic activity.

EP 0 224 722 A1, the entirety of which is herein incorporated by reference, discloses
4 methods for making a variety of substituted pyrimidines which have oral hypoglycemic
activity and suggests their usefulness in the treatment of type II diabetes and/or obesity with
6 associated insulin resistance.

U.S. Patent 5,057,517, the entirety of which is herein incorporated by reference,
8 discloses a variety of 6-piperazinopurines and heteroaromatic derivatives thereof which have
oral hypoglycemic activity and suggests their usefulness in the treatment of type II diabetes
10 and/or obesity with associated insulin resistance. Processes for the preparation of such
compounds and compositions containing such compounds as the active ingredient thereof
12 are also disclosed.

EP 1 258 247 A1 and WO 02/092093 A1, the entireties of which are herein
14 incorporated by reference, describe a variety of adenosine derivatives and suggests their
usefulness in producing medicines for the treatment of the insulin resistance syndrome and
16 diabetes.

US Patent 6,294,522 and Published US Application 2002/0045595A1, the entireties
18 of which are herein incorporated by reference, disclose a variety of N6 heterocyclic 8
modified adenosine derivatives that are selective, partial or full adenosine A1 receptor
20 partial or full agonists and suggests their usefulness for modifying cardiac activity,
modifying adipocyte function, treating central nervous system disorders, and treating
22 diabetic disorders and obesity in mammals, and especially in humans.

WO 01/40246 A1, US Patent 6,258,793 and Published US Application

2 2002/0037872A1, the entireties of which are herein incorporated by reference, disclose a
variety of N6 heterocyclic 5' modified adenosine derivatives that are adenosine A1 receptor
4 partial or full agonists and suggests their usefulness for modifying cardiac activity,
modifying adipocyte function, treating central nervous system disorders, and treating
6 diabetic disorders and obesity in mammals, and especially in humans.

EP 1 054 012 A1 and EP 1 300 147 A1, the entireties of which are herein
8 incorporated by reference, disclose A2 receptor antagonists and their pharmacologically
acceptable salts or hydrates and suggests their usefulness for preparing medicaments for
10 preventing or treating diabetes mellitus or diabetic complications, and for preparing
improving agents for impaired glucose tolerance, potentiating agent for insulin sensitivity or
12 medicaments for preventing or treating obesity.

US Patent 6,525,083, the entirety of which is herein incorporated by reference,
14 discloses methods for making a variety of N-substituted indoles that are agonists or partial
agonists of PPAR gamma and suggests their usefulness in the treatment, control or
16 prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia,
dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis,
18 obesity, vascular restenosis, inflammation, and other PPAR mediated diseases, disorders and
conditions.

20 US Patent 5,547,942, the entirety of which is herein incorporated by reference,
discloses treating patients suffering from NIDDM, and their chronic clinical complications
22 which are the result of continuous hyperglycemia, by the administration of adenine
nucleotides or adenosine and inorganic phosphate.

Inosine and uridine at concentrations of 10^{-5} M have been shown to increase glucose uptake in rabbit hearts (Hait et al., Circulation, 1972, 46(2):333-46, the entirety of which is herein incorporated by reference) and rat diaphragm (Kypson et al., J. Pharmacol. and Exptl. Therapeutics, 1976, 199(3):565-574, the entirety of which is herein incorporated by reference).

US Patent 5,190,948, the entirety of which is herein incorporated by reference, discloses methods comprising administering uridine to diabetic patients for treating certain peripheral complications of diabetes, including neuropathy, retinopathy and peripheral vascularpathy.

US Patent 6,316,426 and Published US Application 2002/0035086A1, the entireties of which are herein incorporated by reference, disclose compositions comprising acyl derivatives of cytidine and uridine and their use in treating hepatopathies, diabetes, heart disease, cerebrovascular disorders, Parkinson's disease, infant respiratory distress syndrome and for enhancement of phospholipid biosynthesis comprising administering the acyl derivatives of the invention to an animal.

Another area of active research in the field of diabetes relates to the potential role of AMP-activated protein kinase (AMPK) in the treatment of the disease. Recent data collected in several laboratories indicate that AMPK plays a key role in regulation of carbohydrate and fat metabolism, serving as "a metabolic master switch" in response to alterations in cellular energy charge. (Winder et al, Am J Physiol, 277: E1-10, 1999, the entirety of which is herein incorporated by reference; Winder, J Appl Physiol, 91:1017-1028, 2001, the entirety of which is herein incorporated by reference). AMPK is known to effect increases in glucose uptake and increases in fatty acid oxidation in skeletal muscle,

increases in fatty acid oxidation, decreases in cholesterol synthesis, and decreases in
2 lipogenesis in the liver. Furthermore, AMPK is known to modulate insulin secretion in
pancreatic islets. AMPK phosphorylates numerous target proteins, and the resulting
4 phosphorylation, in turn, may increase or decrease the rate of the metabolic pathway in
which the protein target plays a regulatory role. One form of AMPK is expressed in the cell
6 nucleus, and recent evidence suggests that AMPK can also influence metabolism by
regulating gene expression.

8 It has also recently been reported that methods to increase intracellular levels of
activated AMPK result in one of a number of beneficial effects, including reducing insulin
10 resistance and glucose concentrations in an organism. For example, WO 01/66146 A1, the
entirety of which is herein incorporated by reference, discloses certain plant extract fractions
12 that have potent hypoglycemic and/or lipid lowering activity, and U.S. Provisional Patent
Application 60/408,887 and WO 02/072148 A1, the entireties of which are herein
14 incorporated by reference, further disclose that the extracts have the property to activate
adenosine 5'-monophosphate-activated protein kinase (AMPK). WO 01/93874 A1, the
16 entirety of which is herein incorporated by reference, discloses administering an AMP-
activated protein kinase (AMPK) activator to reduce insulin resistance in a mammal
18 suffering from obesity, type 2 diabetes, or muscle paralysis. Moreover, WO 02/09726 A1,
the entirety of which is herein incorporated by reference, discloses that long-term usage of
20 AICAR (5-amino, 4-imidazole carboxamide riboside), a known activator of AMPK,
produces sustained metabolic and biological changes in mammals that reduce insulin
22 resistance and suggest the usefulness of such a treatment in patients suffering from diseases

and conditions such as diabetes, hypertension, atherosclerosis, polycystic ovary syndrome
2 and gallstones.

Recent data additionally indicate that activated Akt, a serine/threonine kinase also
4 known in the art as protein kinase B (PKB) or RAC-PK, may contribute to the insulin-
sensitizing effects of thiazolidinediones (TZDs) in human skeletal muscle (Meyer et al.,
6 Diabetes. 2002 Sep;51(9):2691-7, the entirety of which is herein incorporated by reference).
Akt is believed to be activated by insulin-induced cascade and to be involved in stimulation
8 of glucose uptake through GLUT-4. Moreover, Akt-deficient animals (knockout) have
been reported to be severely diabetic and insulin resistant (Cho et al., Science, 292, 1728-
10 1731, 2001, the entirety of which is herein incorporated by reference). In addition, protein
TRB3, which is believed to be a negative regulator of Akt, has been proposed as molecular
12 target for development of new anti-diabetic drugs and to improve functioning of Akt
(Mintminy et al, Science, 300, 1574-77, 2003, the entirety of which is herein incorporated
14 by reference).

Although many methods and compositions are known for modulating various
16 metabolic activities associated with elevated blood glucose and/or blood lipids, all or almost
all of the known methods and compositions suffer from one or more disadvantages.
18 Therefore, a need remains for improved compositions and methods for modulating various
metabolic activities associated with elevated blood glucose and/or blood lipids.

2

SUMMARY OF THE INVENTION

According to the invention, compounds including various purine derivatives and
pyrimidine derivatives have been found to be potent activators of adenosine 5'-
monophosphate-activated protein kinase (AMPK) and/or Akt. Thus, an aspect of the
invention relates to purine derivatives, including cytokinins, adenine derivatives, and
guanine derivatives, as well as to pyrimidine derivatives, including cytosine derivatives, that
are activators of AMPK and/or Akt. In one aspect, the present invention concerns the use of
such activators, as well as compositions comprising such activators, to increase intracellular
levels of activated AMPK and/or activated Akt to result in one of a number of beneficial
effects in an organism. An aspect of the present invention also concerns the use of such
activators, as well as compositions comprising such activators, in the prevention or
treatment of diseases and conditions treatable through increasing intracellular levels of
activated AMPK and/or activated Akt, such as diseases and conditions associated with
elevated blood glucose and/or blood lipids, for example. An aspect of the present invention
is particularly concerned with the treatment of insulin resistance and/or type II diabetes. The
invention provides, among other aspects, an anti-diabetic agent, an anti-diabetic composition
containing the anti-diabetic agent, a foodstuff or beverage containing the anti-diabetic agent,
kits based on the anti-diabetic agent, a method for preventing or treating diabetes or
impaired glucose tolerance, and a method of decreasing blood glucose level. The invention
additionally provides screening methods comprising measuring the ability of a purine
derivative, such as a cytokinin, an adenine derivative, or a guanine derivative, and/or
measuring the ability of a pyrimidine derivative, such as a cytosine derivative, to increase

intracellular levels of activated AMPK and/or activated Akt. The invention additionally
2 provides screening methods comprising measuring the ability of a purine derivative, such as
a cytokinin, an adenine derivative, or a guanine derivative, and/or measuring the ability of a
4 pyrimidine derivative, such as a cytosine derivative, to increase expression and/or function
of the glucose transporter GLUT-4.

6 Various objects, features, aspects and advantages of the present invention will
become more apparent from the following detailed description of preferred embodiments of
8 the contemplated invention.

10 **DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

An advantageous aspect of the instant invention concerns the discovery that, when
12 administered in a therapeutically effective dose, compounds and compositions of the
invention modulate one or more of various metabolic activities. In particularly preferred
14 embodiments of the contemplated invention, when administered in a therapeutically
effective dose, compounds and compositions of the invention will reduce blood glucose
16 concentrations in an organism suffering from an elevated glucose concentration. While not
wishing to be bound by theory, applicants believe a mechanism involving the activation of
18 AMPK and/or Akt underlies the reduction in blood glucose that follows administering a
contemplated compound, or a composition comprising a contemplated compound, to an
20 organism. As such, the utility of the inventive subject matter additionally extends to
methods for treating a variety of disorders that are ameliorated through activation of AMPK
22 and/or Akt, such as those disorders well known in the art and/or exemplified in the instant
application.

2 **A. Terms**

 The term "alkyl" refers to the radical of aliphatic groups, including straight-chain
4 alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted
 cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a
6 straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁
 -C₃₀ for straight chain, C₃ -C₃₀ for branched chain), and more preferably 20 or fewer. A
8 preferred embodiment of an alkyl is a (C₁-C₂₅)alkyl. Another preferred embodiment of an
 alkyl is a (C₁-C₂₀)alkyl. Another preferred embodiment of an alkyl is a (C₁-C₁₅)alkyl. In
10 preferred embodiments, cycloalkyls have from 4-10 carbon atoms in their ring structure, and
 more preferably have 5, 6 or 7 carbons in their ring structure.

12 Moreover, the term "alkyl" as used throughout the specification and claims is
 intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which
14 refers to alkyl moieties having one or more substituents on one or more carbons of the
 hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl,
16 alkylcarbonyloxy, aryl, alkenyl, alkynyl, arylcarbonyloxy, alkoxy alkoxycarbonyloxy,
 aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl,
18 alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including
 alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acyl, heteroacyl,
20 acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido),
 amidino, imino, sulfhydryl, alkylthio, arylthio, alkylsilyl, alkylseleno, thiocarboxylate,
22 sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido,
 heterocyclyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aralkyl, or an aromatic or

heteroaromatic moiety. It will be understood by those skilled in the art that the moieties
2 substituted on the hydrocarbon chain can themselves be substituted, if appropriate.
Cycloalkyls can be further substituted, e.g., with the substituents described above. Preferred
4 embodiments of alkyl groups include those having an aliphatic backbone containing one or
more heteroatoms. Other preferred embodiments of alkyl groups include those having an
6 aliphatic backbone that does not contain a heteroatom. An "aralkyl" moiety is an alkyl
substituted with an aryl (e.g., phenylmethyl (benzyl)). Thus, the term alkyl as used herein,
8 unless otherwise noted, is also meant to include such aralkyl moieties. The term alkyl as
used herein further encompasses heteroalkyls, as defined below.

10 Unless the number of carbons is otherwise specified, "lower alkyl" as used herein
refers to an alkyl group having from one to ten carbons, more preferably from one to six
12 carbon atoms in its backbone structure. Lower alkyls are among especially preferred alkyl
groups. A preferred embodiment of a lower alkyl is a (C₁-C₁₀)alkyl. Another preferred
14 embodiment is a (C₁-C₈)alkyl. Another preferred embodiment is a (C₁-C₆)alkyl. And an
especially preferred alkyl is a (C₁-C₄)alkyl.

16 The terms "alkenyl" and "alkynyl" as used herein refer to unsaturated aliphatic
groups analogous to alkyls as defined above, where alkenyls and alkynyls differ from alkyls
18 in that alkenyls and alkynyls contain at least one double or triple bond, respectively.

Examples of alkenyl residues include, for example, isobutenyl, isopentenyl, vinyl, 1-
20 propenyl, 2-propenyl (=allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl,
5-hexenyl, and 1,3-pentadienyl. Examples of alkynyl residues include ethynyl, 1-propynyl,
22 2-propynyl (=propargyl), and 2-butyne. In a preferred embodiment, a compound comprises

the radical of an unsaturated aliphatic group as an alkyl substituent. For example, an
2 isopentenyl residue could equally be considered methyl residue substituted with isobutenyl.

The term "heteroalkyl" as used herein refers to those alkyls having an aliphatic
4 backbone containing one or more heteroatoms. Examples of heteroalkyl residues include,
for example, methoxymethyl, 3-thiomethylpropyl, and 2-thiomethoxyethoxymethyl and the
6 like. Up to two heteroatoms may be consecutive, such as $-\text{CH}_2\text{-NH-OCH}_3$ and $-\text{CH}_2\text{-O-}$
 $\text{Si}(\text{CH}_3)_3$, for example. In a preferred embodiment, a heteroalkyl includes up to four
8 heteroatoms. In other preferred embodiments, a heteroalkyl contains one, two or three
heteroatoms. In a preferred embodiment, the heteroatom is selected from O, N, S and Si. In
10 another preferred embodiment, the heteroatom is selected from P, B and Se. In a preferred
embodiment, the heteroatom is O. In a preferred embodiment, the heteroatom is N. In a
12 preferred embodiment, the heteroatom is S. In a preferred embodiment, the heteroatom is
Si. A preferred embodiment of an alkyl is a heteroalkyl containing 1 to 29 aliphatic carbon
14 atoms. Another preferred embodiment is a heteroalkyl containing 1 to 19 aliphatic carbon
atoms. A preferred embodiment is a heteroalkyl containing 1 to 9 aliphatic carbon atoms.
16 Another preferred embodiment is a heteroalkyl containing 1 to 7 aliphatic carbon atoms.
Another preferred embodiment is a heteroalkyl containing 1 to 5 aliphatic carbon atoms.
18 Another preferred of an alkyl is a heteroalkyl containing 1 to 3 aliphatic carbon atoms. And
an especially preferred alkyl is a heteroalkyl containing 1 to 2 aliphatic carbon atoms.
20 Likewise, the term "heteroalkenyl" as used herein refers to those alkenyls having an
aliphatic backbone containing one or more heteroatoms, and the term "heteroalkynyl" as
22 used herein refers to those alkynyls having an aliphatic backbone containing one or more
heteroatoms.

example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy,
2 aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl,
alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including
4 alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino
(including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,
6 sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido,
nitro, trifluoromethyl, cyano, azido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic
8 moiety.

The terms "polycyclyl" or "polycyclic group" refer to two or more cyclic rings (e.g.,
10 cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more
carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are
12 joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the
polycycle can be substituted with such substituents as described above, as for example,
14 halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy,
aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl,
16 alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including
alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino
18 (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,
sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido,
20 nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, aralkyl, or an aromatic or
heteroaromatic moiety.

22 The term "acyl" refers to a moiety of the formula $-C(O)R'$, wherein R'
encompasses, for example, hydrogen or an alkyl, aryl, aralkyl or heterocyclyl group. In

preferred embodiments, R' of the acyl group is alkyl, aryl, alkaryl, aralkyl, amino acid
2 residue, heteroaromatic, alkoxyalkyl including methoxymethyl; arylalkyl including benzyl,
aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with
4 halogen, C₁ to C₄ alkyl, or C₁ to C₄ alkoxy, or the residue of an amino acid. Acyl
substituents may be derived from carboxylic acids which include, but are not limited to,
6 compounds selected from the group consisting of a fatty acid, an amino acid, acetic acid,
nicotinic acid, dicarboxylic acids, tricarboxylic acids, citric acid, lactic acid, p-aminobenzoic
8 acid and orotic acid. In preferred embodiments acyl substituents may be derived from
carboxylic acids in which the atom adjacent to the carbonyl carbon atom is another carbon
10 atom. In preferred embodiments acyl substituents may be derived from carboxylic acids in
which the atom adjacent to the carbonyl carbon atom is an oxygen that is furthermore
12 covalently linked to another carbon atom. In a preferred embodiment, the acyl substituents
are substantially nontoxic carboxylic acids. Especially advantageous acyl substituents are
14 carboxylic acids which are normally present in the body, either as dietary constituents or as
intermediary metabolites.

16 The term "heteroacyl" as used herein refers to a moiety of the formula --X(O)R' or
--X(OH)R', wherein X is a heteroatom and R' encompasses, for example, hydrogen or an
18 alkyl, aryl, aralkyl or heterocyclyl groups. In a preferred embodiment, the X is selected
from N, S, P, Si, B or Se. In another preferred embodiment, X is selected from N, S, P and
20 Si. In a more preferred embodiment, the X is selected from N, S and P. In a more preferred
embodiment, the "heteroacyl" is a moiety of the formula --X(O)R', and X is selected from N
22 and S. In a preferred embodiment, X is S. In another preferred embodiment, X is N.

The term "acyl derivative" as used herein means any derivative of a compound in which one or more acyl groups are present. Examples of acyl derivatives are those wherein the hydrogen atom in an --OH group, and/or one or both of the hydrogen atoms in the --NH₂ group, are replaced by an acyl group of --C(O)R', wherein R' may be, as non-limiting examples, hydrogen or an alkyl, aryl, aralkyl, or heterocyclyl group. Likewise, the term "heteroacyl derivative" as used herein refers to any derivative of a compound in which one or more heteroacyl groups are present.

The term "hydrocarbylcarbonyl" as used herein means an acyl radical of a carboxylic acid in which the atom adjacent to the carbonyl carbon atom is another carbon atom. The parent carboxylic acid may, for example, be a fatty acid, an aromatic acid (e.g. benzoate, nicotinoate, or their congeners), an amino acid, a cycloalkylcarboxylic acid, or a dicarboxylic acid.

The term "hydrocarbyloxycarbonyl" as used herein means an acyl radical of a carboxylic acid in which the atom adjacent to the carbonyl carbon atom is oxygen which is furthermore covalently linked to another carbon atom. This can also be described as a radical of a carbonate ester of an alcohol, which, when cleaved from a purine or pyrimidine following administration, degrades further into carbon dioxide and an alcohol. Advantageous alcohols are those which are of low toxicity, particularly those which enter readily into normal metabolic or eliminative pathways.

The term "fatty acids" as used herein means aliphatic carboxylic acids having at least 2 carbon atoms. In one embodiment, such fatty acids have no more than 22 carbon atoms. Such fatty acids may be saturated, partially saturated or polyunsaturated.

The term "amino acids" as used herein encompasses, but is not limited to, glycine,
2 the L or R forms of alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, proline,
hydroxyproline, serine, threonine, cysteine, cystine, methionine, tryptophan, aspartic acid,
4 glutamic acid, arginine, lysine, histidine, ornithine, hydroxylysine, carnitine, and other
naturally occurring amino acids. The L form of these amino acids is an especially preferred
6 embodiment.

The term "dicarboxylic acids" as used herein means fatty acids with a second
8 carboxylic acid substituent.

The term "halogen" is meant to include fluorine, chlorine, bromine and iodine, or
10 fluoro, chloro, bromo, and iodo.

The term "saccharide" is meant to include both aldoses (sugars derived from
12 monosaccharides having an empirical formula $(CH_2O)_n$ where n equals 3 or some larger
number and the monosaccharide has an aldehyde or like group at the end of its chain) and
14 ketoses (derivatives of monosaccharides having a ketone group within its structure other
than at its end). Saccharides also include both the ring and open chain forms and the
16 levorotatory (L) and the dextrorotatory (D) forms and the alpha and the beta forms thereof.
Both substituted and unsubstituted saccharides are encompassed by the term. Preferred
18 substituted saccharides include acyl derivatives.

Examples of saccharides are pentoses, which include ribose, arabinose, xylose,
20 lyxose, ribulose, and xylulose. Preferred pentoses are the pentoses ribose and 2'-
deoxyribose in which the hydroxide group and the 2'-position is replaced by hydrogen. The
22 beta-D forms are also particularly preferred. Other useful saccharides include hexoses such
as allose, altrose, glucose, mannose, gluose, idose, galactose, talose, psicose, fructose,

sorbose, and tagatose. Tetroses include erythrose, threose, and erythrulose. Thus, when in
2 this document reference is made to a chemical whose name includes "saccharide", or
elsewhere where the word saccharide is used it should be understood that the alpha or beta,
4 D or L, and oxy or deoxy forms of saccharides are contemplated. Furthermore, in preferred
embodiments according to the present invention, the term "saccharide" in a name, or the
6 term saccharide in text both refers to ribose or 2'-deoxyribose. The term 5'phospho-ribosyl
will be understood to encompass 5' mono-, di-, and tri-phospho-ribosyl; and the term
8 5'phospho-deoxyribosyl will be understood to encompass 5' mono-, di-, and tri-phospho-
deoxyribosyl.

10 The term "heteroatom" as used herein means an atom of any element other than
carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

12 The term "substantially pure" as used herein, refers to a composition which is
substantially free of impurities, including (but not limited to) starting materials, side
14 products, undesired co-eluting compounds or any other undesired component. A
composition is "substantially pure" when impurities comprise less than about 25% of the
16 composition by weight. In a preferred embodiment, a composition is substantially pure
when impurities comprise less than about 20% of the composition by weight. In a more
18 preferred embodiment, a composition is substantially pure when impurities comprise less
than about 15% of the composition by weight. In a still more preferred embodiment, a
20 composition is substantially pure when impurities comprise less than about 10% of the
composition by weight. In a still more preferred embodiment, a composition is substantially
22 pure when impurities comprise less than about 5% of the composition by weight. In an

especially preferred embodiment, a composition is substantially pure when impurities

2 comprise less than about 1% of the composition by weight.

The term "pharmaceutical composition" refers to a composition comprising as active
4 ingredient(s) one or more contemplated compounds of the invention, such as a purine
derivative or a pyrimidine derivative, or a pharmaceutically acceptable salt, racemate,
6 enantiomer, tautomer, solvate, hydrate, pro-drug and/or polymorph thereof, and may also
optionally contain a pharmaceutically acceptable carrier and optionally other therapeutic
8 ingredients. The compositions may be presented in unit dosage form and prepared by any of
the methods well-known in the art of pharmacy. Dosage regimes may be adjusted for the
10 purpose to improving the therapeutic response. For example, several divided dosages may
be administered daily or the dose may be proportionally reduced over time. A person skilled
12 in the art normally may determine the effective dosage amount and the appropriate regime.

The term "substantially pure pharmaceutical composition" refers to a pharmaceutical
14 composition as defined above, where the one or more contemplated compounds of the
invention, the optional pharmaceutically acceptable carrier, and the optional other
16 therapeutic ingredients comprise, in total, at least about 75% of the composition by weight.

In a preferred embodiment of a substantially pure pharmaceutical composition, one or more
18 contemplated compounds of the invention, the optional pharmaceutically acceptable carrier,
and the optional other therapeutic ingredients comprise, in total, at least about 85% of the
20 composition by weight. In a more preferred embodiment of a substantially pure
pharmaceutical composition, one or more contemplated compounds of the invention, the
22 optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients
comprise, in total, at least about 90% of the composition by weight. In a still more preferred

embodiment of a substantially pure pharmaceutical composition, one or more contemplated
2 compounds of the invention, the optional pharmaceutically acceptable carrier, and the
optional other therapeutic ingredients comprise, in total, at least about 95% of the
4 composition by weight. In an especially preferred embodiment of a substantially pure
pharmaceutical composition, one or more contemplated compounds of the invention, the
6 optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients
comprise, in total, at least about 99% of the composition by weight.

8 The phrase "pharmaceutically acceptable" is employed herein to refer to those
compounds, materials, compositions and/or dosage forms which are, within the scope of
10 sound medical judgment, suitable for use in contact with the tissues of human beings and
animals without excessive toxicity, irritation, allergic response, or other problem or
12 complication, commensurate with a reasonable benefit/risk ratio.

 The term "pharmaceutically acceptable carrier" encompasses any of the standard
14 pharmaceutical carriers, diluents, buffers, excipients, solid fillers, and the like, including (1)
fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid;
16 (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl
pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating
18 agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain
silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6)
20 absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such
as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and
22 bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid
polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) coloring agents: (11)

phosphate-buffered saline solution (12) emulsions, such as an oil/water or water/oil
2 emulsion; (12) adjuvants; and (13) sterile aqueous solutions, for example. Each carrier must
be "acceptable" in the sense of being compatible with the other ingredients of the
4 formulation and not injurious to the patient. Some additional examples of materials which
can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose,
6 glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its
derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate;
8 (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter
and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil,
10 olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such
as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and
12 ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum
hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's
14 solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic
compatible substances employed in pharmaceutical formulations. Additional suitable
16 pharmaceutical carriers and their formulations are described in REMINGTON'S
PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, 19th ed. 1995, the
18 entirety of which is herein incorporate by reference) as well as in US Patent 6,416,965, the
entirety of which is herein incorporated by reference). As one of skill in the art would
20 recognize, a "carrier" that comprises substantial amounts of unknown compounds and/or
impurities is not preferred for pharmaceutical use. Thus, preferred pharmaceutically
22 acceptable carriers are, therefore, those in which such unknown compounds and/or
impurities comprise, in total, less than about 25% of the carrier by weight. More preferred

pharmaceutically acceptable carriers are those in which such unknown compounds and/or
2 impurities comprise, in total, less than about 20% of the carrier by weight. Still more
preferred pharmaceutically acceptable carriers are those in which such unknown compounds
4 and/or impurities comprise, in total, less than about 20% of the carrier by weight. Still
more preferred pharmaceutically acceptable carriers are those in which such unknown
6 compounds and/or impurities comprise, in total, less than about 15% of the carrier by
weight. Still more preferred pharmaceutically acceptable carriers are those in which such
8 unknown compounds and/or impurities comprise, in total, less than about 10% of the carrier
by weight. Still more preferred pharmaceutically acceptable carriers are those in which such
10 unknown compounds and/or impurities comprise, in total, less than about 5% of the carrier
by weight. Especially preferred pharmaceutically acceptable carriers are those in which
12 such unknown compounds and/or impurities comprise, in total, less than about 1% of the
carrier by weight.

14 The term "pharmaceutically acceptable salt" is intended to encompass all acceptable
salts that can be used for modifying the solubility or hydrolysis characteristics or can be
16 used in sustained release or pro-drug formulations. Certain embodiments of the present
compounds may contain a basic functional group, such as amino or alkylamino, and are,
18 thus, capable of forming pharmaceutically acceptable salts with pharmaceutically-acceptable
acids. Thus, the term "pharmaceutically acceptable salts" encompasses the relatively non-
20 toxic, inorganic and organic acid addition salts of compounds of the present invention.

These salts can be prepared *in situ* during the final isolation and purification of the
22 compounds of the invention, or by separately reacting a purified compound of the invention
in its free base form with a suitable organic or inorganic acid, and isolating the salt thus

formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate,
2 phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate,
phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphylate, mesylate,
4 glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al.
(1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19) In other cases, the compounds of the
6 present invention may contain one or more acidic functional groups and, thus, are capable of
forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. Thus,
8 the term "pharmaceutically acceptable salts" encompasses the relatively non-toxic, inorganic
and organic base addition salts of compounds of the present invention. These salts can
10 likewise be prepared *in situ* during the final isolation and purification of the compounds, or
by separately reacting the purified compound in its free acid form with a suitable base, such
12 as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal action,
with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary
14 amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium,
calcium, magnesium, and aluminum salts and the like. Representative organic amines useful
16 for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine,
ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al.,
18 *supra*) As one of skill in the art would recognize, where a compound is a salt, reference to
"a salt thereof" denotes alternative acceptable salts of the compound, including
20 pharmaceutically acceptable salts of the compound. For example, reference to the salt of
N6 – benzyladenine hydrochloride denotes salts of N6 – benzyladenine comprising an
22 acceptable alternative to the hydrochloride salt. Similarly, where a given compound is a

pharmaceutically acceptable salt, reference to "a pharmaceutically acceptable salt thereof"

2 denotes alternative pharmaceutically acceptable salts of the given compound.

The term "pro-drug" as used herein refers to a derivative of a compound that can
4 hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to
provide a contemplated compound of the invention. A preferred embodiment of a pro-drug is
6 a compound that can hydrolyze, oxidize, or otherwise react under biological conditions to
result in a cytokinin of structure (I), an adenine derivative of structure (II), a guanine
8 derivative of structure (III), or a cytosine derivative of structure (IV). For example,
carboxylic esters are conveniently formed by esterifying carboxylic acid functionalities; if
10 the contemplated compound includes an acid functional group it can be esterified to provide
a pro-drug. Various pro-drugs are well known in the art (For examples of pro-drugs, see:
12 Design of Prodrugs, edited by H. Bundgaard, Elsevier, 1985; Methods in Enzymology, vol.
42, p. 309-396, edited by K. Widder et al., Academic Press, 1985; A Textbook of Drug
14 Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, chapter 5,
"Design and Application of Prodrugs," by H. Bundgaard, p. 113-191, 1991; H. Bundgaard,
16 Advanced Drug Delivery Reviews," 8, 1-38, 1992; H. Bundgaard et al., Journal of
Pharmaceutical Sciences, 77, 285, 1988; and N. Kakeya et al., Chem. Phar. Bull., 32, 692,
18 1984).

The term "therapeutically effective amount" as used herein refers to an amount that
20 provides therapeutic effects for a given condition and administration regime. The amount
will vary with the condition being treated, the stage of advancement of the condition, and the
22 type and concentration of formulation applied. Appropriate amounts in any given instance

will be readily apparent to those skilled in the art or capable of determination by routine
2 experimentation.

The term "patient" as used herein refers to a mammal which is being treated
4 prophylactically and/or for a condition having visible and/or otherwise measurable
symptoms. Preferably the patient is a human. In a preferred embodiment, the patient is a
6 patient receiving treatment under the direction of a healthcare professional. Preferred
embodiments also include patients receiving self-directed treatment.

8 The term "coadministered" as used herein means that at least two of the compounds
of the invention are administered during a time frame wherein the respective periods of
10 pharmacological activity overlap. In a preferred embodiment, a compound is administered
at a time when the pharmacological activity of a previously administered compound is at
12 least half-maximal. In another preferred embodiment, when at least two compounds of the
invention are administered, the duration of time between administering the first and second
14 compounds does not exceed the half-life ($t_{1/2}$) of the first administered compound.

The term "unit dosage" as used herein refers to a physically discrete unit, suitable for
16 oral or parenteral administration, containing an individual quantity of the active component
in association with a pharmaceutically acceptable carrier or diluent, the quantity of the
18 active component being such that at least one unit or severable fraction of a unit is required
for a single therapeutic administration. In the case of severable units, such as scored tablets,
20 at least one severable fraction such as one-half or one-quarter of the unit may be all that is
required for a single therapeutic administration. It will be appreciated that the term "unit
22 dosage" does not include mere powders or solutions except when the powders or solutions
have been prepared so as to be suitable for oral administration, e.g., in capsules, cachets,

pills, tablets, lozenges or other measured forms suitable for oral ingestion, or have been
2 prepared so as to be suitable for parenteral administration, e.g., in vials of a solution suitable
for parenteral injection. The compounds of the invention may be administered alone or in
4 combination with pharmaceutically acceptable carriers or diluents, in either single or
multiple doses. Pharmaceutical compositions are preferably administered in unit dosage
6 form.

The terms "parenteral administration" and "administered parenterally" as used herein
8 means modes of administration other than enteral and topical administration, usually by
injection, and includes, without limitation, intravenous, intramuscular, intraarterial,
10 intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal,
transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid,
12 intraspinal and intrasternal injection and infusion.

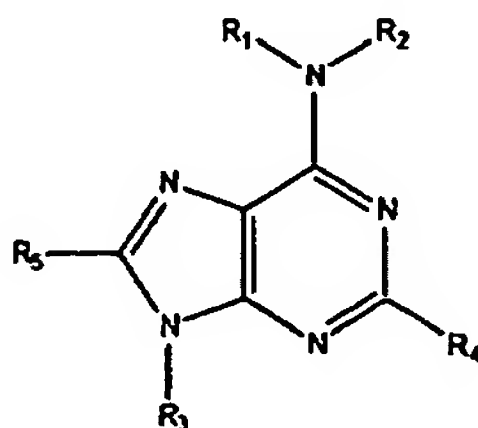
The terms "systemic administration," "administered systemically," "peripheral
14 administration" and "administered peripherally" as used herein mean the administration of a
compound, drug or other material other than directly into the central nervous system, such
16 that it enters the patient's system and, thus, is subject to metabolism and other like processes,
for example, subcutaneous administration.

18 The term "tissue" is intended to include intact cells, blood, blood preparations such
as plasma and serum, bones, joints, muscles, smooth muscles, and organs, both *in vivo* and
20 *in vitro*.

As used herein, the term "AICAR" refers to 5'-aminoimidazole 4-carboxamide 1-
22 ribonucleotide.

The term "cytokinin" is well known to those of skill in the art. For example, various cytokinin compounds have been described in the following articles, the entirety of each of which is herein incorporated by reference: "Cytokinins", Annual Review of Plant Physiology, Vol. 21, 1970, pages 359-383, authored by Skoog and Armstrong; in the article entitled "Cytokinins: Syntheses, Mass Spectra and Biological Activity of Compounds Related to Zeatin", Proceedings of the National Academy of Science, Vol. 63, No. 1, 1969, pages 175-185, by Leonard, Hecht, Skoog and Schmitz; in the article entitled "Cytokinins Influence of Side-Chain Planarity of N6-Substituted Adenines and Adenosines On Their Activity in Promoting Cell Growth", Phytochemistry, Vol. 9, 1970, pages 1907-1913, by Hecht, Leonard, Schmitz and Skoog; and in the article entitled "Cytokinins: Structure/Activity Relationships", Phytochemistry, Vol. 6, 1967, pages 1169-1192, by Skoog, Hamzi, Szweykowska et al. See also Letham (pp. 205-264 in Phytohormones and Related Compounds, Vol. I, D. S. Letham et al, eds., 1978), Chen (Physiologia Plantarum Vol. 101, 1997, pages 665-673) and US Patent 4,581,056, the entirety of each of which is herein incorporated by reference.

As used herein, the term "cytokinin" is a generic name encompassing naturally occurring and synthetic chemical substances that can generally be classified as purine derivatives having the following structure:



wherein:

- 2 - R₁ is H;
- R₂ is alkyl, lower alkyl or alkenyl, preferably (C₁-C₁₀)alkyl or (C₂-
4 C₁₀)alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl or saccharide, preferably ribosyl,
6 deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl,
8 lower alkyl or alkenyl.

10 Moreover, the term "cytokinin" is herein defined to further encompass racemates,
 enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs and/or salts, including
12 pharmaceutically acceptable salts, of a cytokinin as defined by the structure immediately
 above. In a preferred embodiment, cytokinins are naturally occurring. Preferred
14 embodiments of cytokinins include racemates, enantiomers, tautomers, solvates, hydrates,
 pro-drugs, polymorphs and/or salts (including alternative salts, as well as pharmaceutically
16 acceptable salts, and alternative pharmaceutically acceptable salts), acyl derivatives and/or
 heteroacyl derivatives of those cytokinins that are naturally occurring. In a preferred
18 embodiment, cytokinins are synthetic chemical substances that are non-naturally occurring.
 Preferred embodiments of cytokinins include racemates, enantiomers, tautomers, solvates,
20 hydrates, pro-drugs, polymorphs and/or salts (including alternative salts, as well as
 pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts), acyl
22 derivatives and/or heteroacyl derivatives of those cytokinins that are non-naturally
 occurring. Moreover, the term "cytokinin" is herein expressly defined to encompass each of

the following compounds, as well as racemates, enantiomers, tautomers, solvates, hydrates,
2 pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically
acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives
4 and/or heteroacyl derivatives thereof: N6 – benzyladenine; N6 – benzyladenine
hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-
6 7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine;
N6 – benzyladenosine-5'-monophosphate sodium salt; dihydrozeatin; dihydrozeatin
8 hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -
D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside;
10 dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-
isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-
12 isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside;
N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-
14 methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-
isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride;
16 kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt;
meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-
18 topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin;
cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-
20 glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin
riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-
22 methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside.

As used herein, the term "AMPK" refers to adenosine 5'-monophosphate-activated
2 protein kinase, an enzyme well known in the art (See, for example, Fryer et al, Biochem J.
2002 Apr 1;363(Pt 1):167-74, the entirety of which is herein incorporated by reference).

4 As used herein the term "compound that activates AMPK" refers to any compound
that, when placed in contact with an appropriate cell or organism, increases phosphorylation
6 of AMPK and/or increases phosphorylation by AMPK of any one of its numerous protein
targets. (Winder et al, Am J Physiol, 277: E1-10, 1999, the entirety of which is herein
8 incorporated by reference) The term is not limited by the mechanism underlying how the
phosphorylation of AMPK and/or phosphorylation by AMPK is increased. The potential
10 mechanisms through which such a compound may act include, but are not limited to,
allosteric mechanisms that affect, directly or indirectly, AMPK activity, as well as
12 mechanisms that act, directly or indirectly, to promote activation of AMPK catalytic activity
through phosphorylation of AMPK catalyzed by a distinct upstream kinase, such as by
14 AMPK kinase (AMPKK). Among other potential mechanisms, such a compound may
prevent or reduce the inhibition of AMPK activity exerted through proteins that otherwise
16 inhibit the activity of AMPK.

As used herein, the term "Akt" refers to a serine/threonine kinase that is also known
18 in the art as protein kinase B (PKB) or RAC-PK (See, for example, Brazil and Hemmings,
Trends Biochem Sci 2001 Nov;26(11):657-64, the entirety of which is herein incorporated
20 by reference).

As used herein the term "compound that activates Akt" refers to any compound that,
22 when placed in contact with an appropriate cell or organism, increases phosphorylation of
Akt and/or increases phosphorylation by Akt of any one of its numerous protein targets.

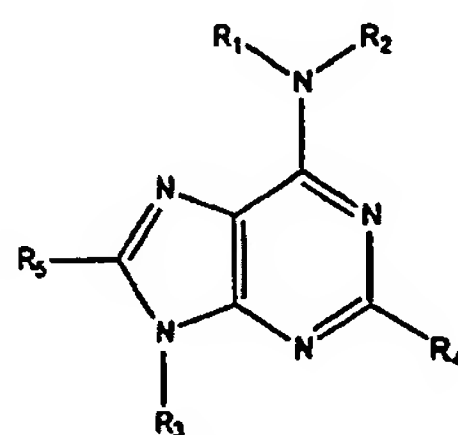
The term is not limited by the mechanism underlying how the phosphorylation of Akt and/or phosphorylation by Akt is increased. The potential mechanisms through which such a compound may act include, but are not limited to, allosteric mechanisms that affect, directly or indirectly, Akt activity, as well as mechanisms that act, directly or indirectly, to promote activation of Akt catalytic activity through phosphorylation of Akt catalyzed by a distinct upstream kinase. Among other potential mechanisms, such a compound may prevent or reduce the inhibition of Akt activity exerted through proteins that otherwise inhibit the activity of Akt.

As used herein, the term “elevated glucose concentration” refers to a concentration that is above the clinical range considered normal (*i.e.*, in humans, above a fasting glucose concentration of about 110 mg/dl). Similarly, the term “elevated lipid concentration” refers to a concentration of blood lipids that is above the clinical range considered normal.

B. Compounds of the Invention

Cytokinins

Contemplated compounds of the invention include cytokinins having the following structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

2 and/or pharmaceutically acceptable salt thereof,

wherein:

- 4 - R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- 6 - R₃ is hydrogen, alkyl, lower alkyl or saccharide, preferably ribosyl,
deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- 8 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl,
lower alkyl alkenyl or alkynyl.

10

Particularly preferred cytokinins include those compounds of the aforementioned
12 structure (I) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof, wherein:

- 14 - R₁ is hydrogen or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-
16 C₁₀)alkyl, (C₁-C₈)alkyl, (C₁-C₇)alkyl), (C₁-C₆)alkyl, (C₁-C₄)alkyl or
heteroalkyl) or alkenyl (preferably (C₂-C₃₀)alkenyl, (C₂-C₂₀)alkenyl, (C₂-
18 C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₂-C₇)alkenyl), (C₂-C₅)alkenyl), (C₂-
C₄)alkenyl) or heteroalkenyl), either unsubstituted or substituted with one or
20 more of: hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl
(preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl (preferably (C₂-C₇)alkenyl
22 or heteroalkenyl); alkynyl (preferably (C₂-C₇)alkynyl or heteroalkynyl); acyl;
heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl;

- 2 cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or
cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl,
cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl,
4 pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-
6 ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl
8 (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-
C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-
10 C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
heteroalkenyl).

12

Particularly preferred cytokinins include those compounds of the aforementioned
14 structure (I) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof, wherein:

- 16 - R₁ is hydrogen or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkenyl (preferably (C₂-C₁₀)alkenyl or (C₂-C₇)alkenyl or heteralkenyl),
18 either unsubstituted or substituted with one or more: hydroxy; halogen
(preferably chloro, fluoro and/or bromo); alkyl (preferably (C₁-C₇)alkyl or
20 heteroalkyl); alkenyl (preferably (C₂-C₇)alkenyl or heteroalkenyl); alkynyl
(preferably (C₂-C₇)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl
22 (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably
cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl

- (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl);
- 2 and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- 4 - R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- 6 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
- 8 heteroalkyl).
- 10
- 12 Particularly preferred embodiments of the aforementioned structure (I) include those cytokinins having R₁, R₂, R₃, R₄ and R₅ as defined in Table 1:

2

Table 1 – Preferred Cytokinins

Structure	R ₁	R ₂	R ₃	R ₄	R ₅
(I-a)	H	Isopentenyl	H	H	H
(I-b)	H	Furfuryl	H	H	H
(I-c)	H	Benzyl	Glucosyl	H	H
(I-d)	H	Benzyl	H	H	H
(I-e)	H	Isopentenyl	Ribosyl	H	H
(I-f)	H	Isopentenyl	Glucosyl	H	H
(I-g)	H	Isopentenyl	Glucosyl	Methylthio	H
(I-h)	H	Isopentenyl	5'-phospo-ribosyl	H	Methylthio
(I-i)	H	Benzyl	Ribosyl	H	H
(I-j)	H	Benzyl	5'-phospo-ribosyl	Methyl	H
(I-k)	H	Benzyl	Ribosyl	Methylthio	H
(I-l)	H	Isopentenyl	H	Methylthio	H
(I-m)	H	Furfuryl	Ribosyl	H	H
(I-n)	H	Benzyl	5'-phospo-ribosyl	H	Methyl

4

Contemplated cytokinins further encompass racemates, enantiomers, tautomers,

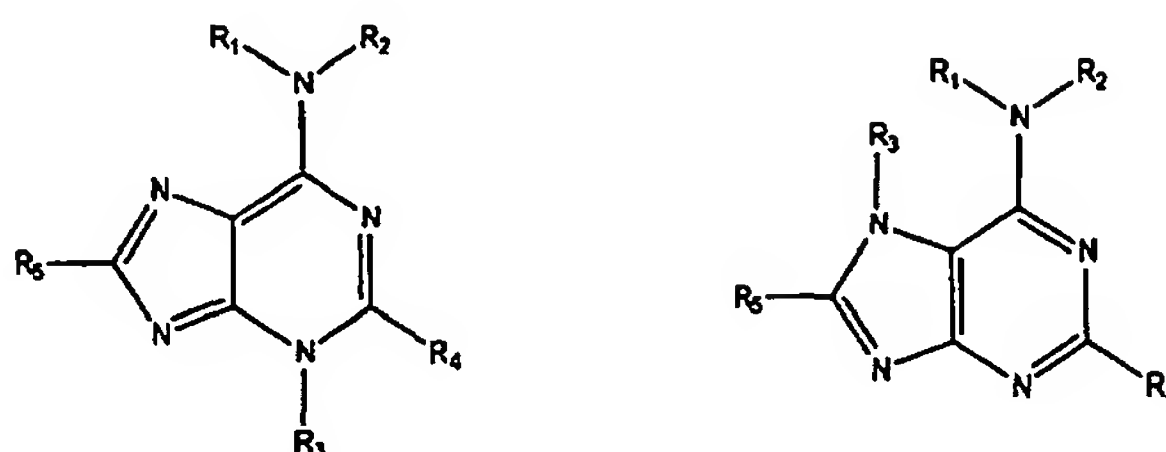
solvates, hydrates, pro-drugs, polymorphs salts (including pharmaceutically acceptable

6

salts), acyl derivatives and/or heteroacyl derivatives of a cytokinin as defined by the above

structure (I). Particularly preferred tautomers of structure (I) are those cytokinins having

2 the following structures:



4 and/or a racemate, enantiomer, solvate, hydrate, pro-drug, polymorph and/or
pharmaceutically acceptable salt thereof,

6 wherein R₁, R₂, R₃, R₄ and R₅ are as defined in any above embodiment of a cytokin
having aforementioned structure (I) and/or a racemate, enantiomer, tautomer,
8 solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable
salt thereof.

10 In a preferred embodiment of the contemplated invention, contemplated cytokinins

12 are naturally occurring. In a preferred embodiment of the contemplated invention,
cytokinins are hydrates, solvates, tautomers, salts (including alternative salts, as well as
14 pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts), acyl
derivatives and/or heteroacyl derivatives of those cytokinins that are naturally occurring. In
16 a preferred embodiment of the contemplated invention, cytokinins are synthetic chemical
substances that are non-naturally occurring. In a preferred embodiment of the contemplated
18 invention, cytokinins are hydrates, solvates, tautomers, salts (including alternative salts, as
well as pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts),

acyl derivatives and/or heteroacyl derivatives of such cytokinins that are non-naturally
2 occurring synthetic chemical substances. Contemplated cytokinins further encompass each
of the following compounds, as well as enantiomers, tautomers, solvates, hydrates, pro-
4 drugs, polymorphs, salts (or alternative salts where the cytokinin is a salt), acyl derivatives
and/or heteroacyl derivatives thereof: N6 – benzyladenine; N6 – benzyladenine
6 hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-
7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine;
8 N6 – benzyladenosine-5'-monophosphate sodium salt; dihydrozeatin; dihydrozeatin
hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -
10 D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside;
dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-
12 isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-
isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside;
14 N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-
methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-
16 isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride;
kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt;
18 meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-
topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin;
20 cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-
glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin
22 riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-
methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside.

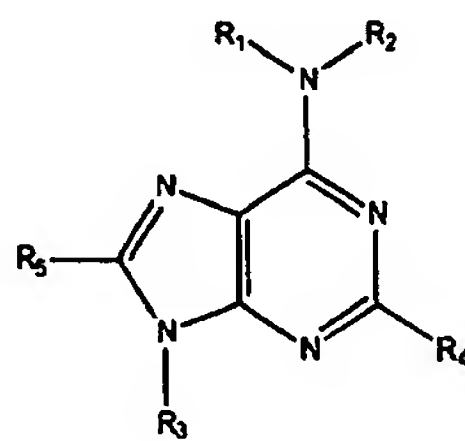
Preferred embodiments of contemplated cytokinins include N6-gamma, gamma-
2 dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-
adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-
4 furfurylaminopurine) and kinetin riboside. Preferred embodiments of contemplated
cytokinins further include acyl derivatives of one or more of N6-gamma, gamma-dimethyl-
6 allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-
isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-
8 furfurylaminopurine) and kinetin riboside. Particularly preferred embodiments of
contemplated cytokinins further include mono-acyl derivatives of one or more of N6-
10 gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-
isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine,
12 kinetin (6-furfurylaminopurine) and kinetin riboside. Preferred embodiments of
contemplated cytokinins further include heteroacyl derivatives of one or more of N6-
14 gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-
isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine,
16 kinetin (6-furfurylaminopurine) and kinetin riboside. Other preferred embodiments of
contemplated cytokinins include mono-heteroacyl derivatives of one or more of N6-gamma,
18 gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-
isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine,
20 kinetin (6-furfurylaminopurine) and kinetin riboside.

Additional preferred embodiments of the contemplated invention include racemates,
22 enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including
alternative salts, as well as pharmaceutically acceptable salts, including alternative

pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of
the aforementioned cytokinins described in this subsection ("Cytokinins").

Adenine Derivatives

Contemplated compounds of the invention include derivatives of adenine defined by
the following structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,

2 deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

4 Preferred derivatives of adenine include those compounds of the aforementioned
formula (II) wherein:

- 6 - R₁ and R₂ are the same or different and are hydrogen or alkyl (preferably (C₁-
C₁₀)alkyl or (C₁-C₇)alkyl or heteroalkyl), either unsubstituted or substituted
8 with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo);
alkyl (preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl (preferably (C₂-
10 C₇)alkenyl or heteroalkenyl); alkynyl (preferably (C₂-C₇)alkynyl or
heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl);
12 alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl
and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl,
14 cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl,
pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
16 - R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-
ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
18 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl
(preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-
20 C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-
C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
22 heteroalkyl);

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of adenine include those compounds of the aforementioned
structure (II) wherein:

- R₁ and R₂ are the same or different and are hydrogen or alkenyl (preferably (C₂-C₁₀)alkenyl or (C₂-C₇)alkenyl or heteralkenyl), either unsubstituted or substituted with one or more of hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl (preferably (C₂-C₇)alkenyl or heteroalkenyl); alkynyl (preferably (C₂-C₇)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or heteroalkyl);

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

2 wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

4

Particularly preferred derivatives of adenine include those compounds of the
6 aforementioned structure (II) wherein:

- R₁ and R₂ are the same or different and are hydrogen or acyl;
- 8 - R₃ is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-
ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- 10 - R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl or
alkenyl;

12 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
14 deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

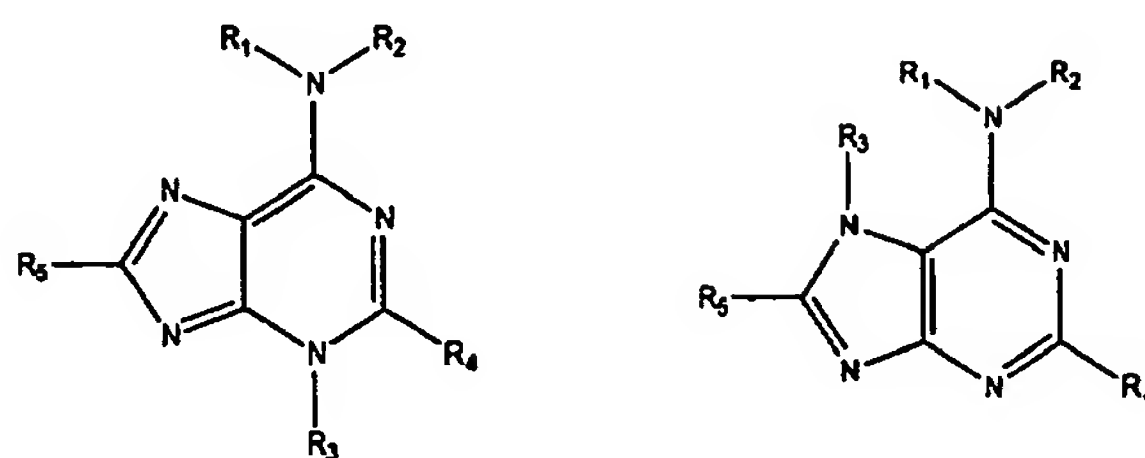
16 Particularly preferred embodiments of the aforementioned structure (II) include those
derivatives of adenine having R₁, R₂, R₃, R₄ and R₅ as defined in Table 2:

2

Table 2 – Preferred Adenine Derivatives

Structure	R ₁	R ₂	R ₃	R ₄	R ₅
(II-a)	Acyl	H	H	H	H
(II-b)	Acyl	H	Saccharide	H	H
(II-c)	Acyl	Alkyl	H	H	H
(II-d)	Acyl	Alkyl	Saccharide	H	H
(II-e)	Acyl	H	H	Alkyl	H
(II-f)	Acyl	H	H	Alkyl	Alkyl
(II-g)	Heteroacyl	H	Saccharide	H	H
(II-h)	Aryl	H	H	H	H
(II-i)	Aryl	H	Saccharide	H	H
(II-j)	Aryl	Alkyl	H	H	H
(II-k)	Aryl	Alkyl	Saccharide	H	H
(II-l)	Aryl	H	H	Alkyl	H
(II-m)	Alkyl	H	H	H	H
(II-n)	Alkyl	H	Saccharide	H	H
(II-o)	Alkyl	Alkyl	H	H	H
(II-p)	Alkyl	Alkyl	Saccharide	H	H
(II-q)	Alkyl	H	H	Alkyl	H

Particularly preferred tautomers of structure (II) are those adenine derivatives having
2 the following structures:



4 and/or a racemate, enantiomer, solvate, hydrate, pro-drug, polymorph and/or
pharmaceutically acceptable salt thereof,
6 wherein R₁, R₂, R₃, R₄ and R₅ are as defined in any above embodiment of an adenine
derivatives having aforementioned structure (II) and/or a racemate,
8 enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or
pharmaceutically acceptable salt thereof.

10

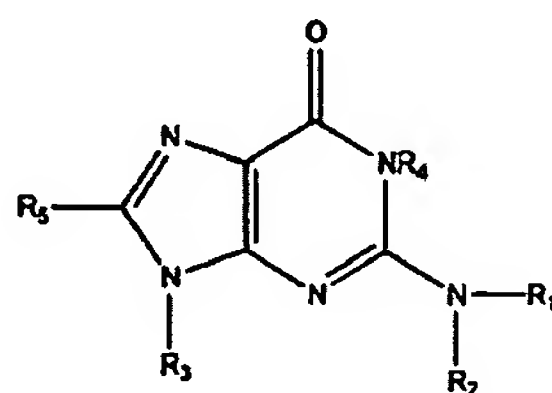
Preferred embodiments of contemplated adenine derivatives include acyl-adenosines
12 and acyl-adenines. Particularly preferred embodiments of contemplated adenine derivatives
are mono-acyl-adenosines and mono-acyl-adenines. Preferred embodiments of
14 contemplated adenine derivatives include heteroacyl-adenosines and heteroacyl-adenines.
Preferred embodiments of contemplated adenine derivatives include mono-heteroacyl-
16 adenosines and mono-heteroacyl-adenines. Particularly preferred embodiments of
contemplated adenine derivatives further include N6-acyl-adenine and N6-acyl-adenosine.
18 Particularly preferred embodiments of contemplated adenine derivatives further include N6-
heteroacyl-adenine and N6-heteroacyl-adenosine. Especially preferred embodiments of

contemplated adenine derivatives further include N6-acetyl-adenine and N6-acetyl-adenosine.

Additional preferred embodiments contemplated by the instant invention include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of the aforementioned contemplated derivatives of adenine described in this subsection ("Adenine Derivatives").

Guanine Derivatives

Contemplated compounds of the invention additionally include derivatives of guanine defined by the following structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

2 - R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl,
heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-
ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and

4 - R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl,
alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

6 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

8 wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

10 Preferred derivatives of guanine include those compounds of the aforementioned
structure (III) wherein:

12 - R₁ and R₂ are the same or different and are hydrogen or alkyl (preferably (C₁-
C₁₀)alkyl or (C₁-C₇)alkyl or heteroalkyl), either unsubstituted or substituted
14 with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo);

16 alkyl (preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl (preferably (C₂-
C₇)alkenyl or heteroalkenyl); alkynyl (preferably (C₂-C₇)alkynyl or

18 heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl);

20 alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl
and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl,

22 cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl,
pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);

22 - R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-
ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and

2 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl
 (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-
 C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-
4 C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
 heteroalkyl);

6 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

 wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
8 deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

10 Preferred derivatives of guanine include those compounds of the aforementioned
 structure (III) wherein:

12 - R₁ and R₂ are the same or different and are hydrogen or alkenyl (preferably
 (C₂-C₁₀)alkenyl or (C₂-C₇)alkenyl or heteralkenyl), either unsubstituted or
14 substituted with one or more of hydroxy; halogen (preferably chloro, fluoro
 and/or bromo); alkyl (preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl
16 (preferably (C₂-C₇)alkenyl or heteroalkenyl); alkynyl (preferably (C₂-
 C₇)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or
18 naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl,
 cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl,
20 cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic
 (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or
22 morpholino);

- R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-
2 ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
 - R₄ and R₅ are the same or different and are individually hydrogen, alkyl
4 (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-
C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-
6 C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
heteroalkyl);
- 8 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and
wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
10 deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

12 Particularly preferred derivatives of guanine include those compounds of the
aforementioned structure (III) wherein:

- R₁ and R₂ are the same or different and are hydrogen or acyl;
- R₃ is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-
16 ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl or
18 alkenyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

20 wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred embodiments of the aforementioned structure (III) include

- 2 those derivatives of guanine having R₁, R₂, R₃, R₄ and R₅ as defined in Table 3:

Table 3 – Preferred Guanine Derivatives

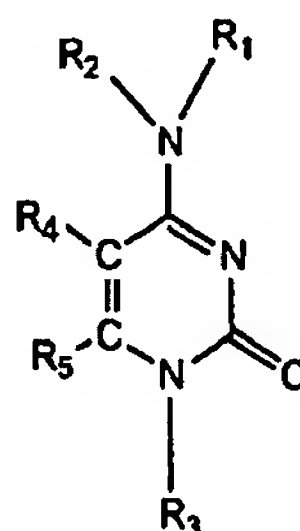
Structure	R ₁	R ₂	R ₃	R ₄	R ₅
(III-a)	Acyl	H	H	H	H
(III-b)	Acyl	H	Saccharide	H	H
(III-c)	Acyl	Alkyl	H	H	H
(III-d)	Acyl	Alkyl	Saccharide	H	H
(III-e)	Acyl	H	H	H	Alkyl
(III-f)	Acyl	H	H	Alkyl	Alkyl
(III-g)	Heteroacyl	H	Saccharide	H	H
(III-h)	Aryl	H	H	H	H
(III-i)	Aryl	H	Saccharide	H	H
(III-j)	Aryl	Alkyl	H	H	H
(III-k)	Aryl	Alkyl	Saccharide	H	H
(III-l)	Aryl	H	H	H	Alkyl
(III-m)	Alkyl	H	H	H	H
(III-n)	Alkyl	H	Saccharide	H	H
(III-o)	Alkyl	Alkyl	H	H	H
(III-p)	Alkyl	Alkyl	Saccharide	H	H
(III-q)	Alkyl	H	H	H	Alkyl

Preferred embodiments of contemplated guanine derivatives include acyl-guanines
2 and acyl-guanosines. Particularly preferred embodiments of contemplated guanine
derivatives mono-acyl-guanines and mono-acyl-guanosines. Preferred embodiments of
4 contemplated guanine derivatives include heteroacyl-guanines and heteroacyl-guanosines.
Preferred embodiments of contemplated guanine derivatives include mono-heteroacyl-
6 guanines and mono-heteroacyl-guanosines. Particularly preferred embodiments of
contemplated guanine derivatives further include N2-acyl-guanine and N2-acyl-guanosine.
8 Particularly preferred embodiments of contemplated guanine derivatives further include N2-
heteroacyl-guanine and N2-heteroacyl-guanosine. Especially preferred embodiments of
10 contemplated guanine derivatives further include N2-acetyl-guanine and N2-acetyl-
guanosine.

12 Additional preferred embodiments contemplated by the instant invention
includeracemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts
14 (including alternative salts, as well as pharmaceutically acceptable salts, including
alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives
16 of any of the aforementioned contemplated derivatives of guanine described in this
subsection ("Guanine Derivatives").

Cytosine Derivatives

2 Contemplated compounds of the invention include derivatives of cytosine defined by
the following structure:



(IV)

6 and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

8 wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl,
10 alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl,
12 heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-
ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl,
14 alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

16 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

18 wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of cytosine include those compounds of the aforementioned

2 structure (IV) wherein:

- R₁ and R₂ are the same or different and are hydrogen or alkyl (preferably (C₁-
4 C₁₀)alkyl or (C₁-C₇)alkyl or heteroalkyl), either unsubstituted or substituted
with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo);
6 alkyl (preferably (C₁-C₇)alkyl or heteroalkyl); alkenyl (preferably (C₂-
C₇)alkenyl or heteroalkenyl); alkynyl (preferably (C₂-C₇)alkynyl or
8 heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl);
alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl
10 and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl,
cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl,
12 pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R₃ is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-
14 ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl
16 (preferably (C₁-C₃₀)alkyl, (C₁-C₂₀)alkyl, (C₁-C₁₅)alkyl, (C₁-C₁₀)alkyl, (C₁-
C₇)alkyl) or heteroalkyl) or alkenyl (preferably (C₁-C₃₀)alkenyl, (C₁-
18 C₂₀)alkenyl, (C₁-C₁₅)alkenyl, (C₁-C₁₀)alkenyl, (C₁-C₇)alkenyl) or
heteroalkyl);

20 wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,

22 deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of cytosine include those compounds of the aforementioned

2 structure (IV) wherein:

- 3 R_1 and R_2 are the same or different and are hydrogen or alkenyl (preferably

4 (C_2-C_{10}) alkenyl or (C_2-C_7) alkenyl or heteralkenyl), either unsubstituted or

5 substituted with one or more of hydroxy; halogen (preferably chloro, fluoro

6 and/or bromo); alkyl (preferably (C_1-C_7) alkyl or heteroalkyl); alkenyl

7 (preferably (C_2-C_7) alkenyl or heteroalkenyl); alkynyl (preferably $(C_2-$

8 $C_7)$ alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or

9 naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl,

10 cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl,

11 cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic

12 (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or

13 morpholino);
- 14 R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-

15 ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- 16 R_4 and R_5 are the same or different and are individually hydrogen, alkyl

17 (preferably (C_1-C_{30}) alkyl, (C_1-C_{20}) alkyl, (C_1-C_{15}) alkyl, (C_1-C_{10}) alkyl, $(C_1-$

18 $C_7)$ alkyl) or heteroalkyl) or alkenyl (preferably (C_1-C_{30}) alkenyl, $(C_1-$

19 $C_{20})$ alkenyl, (C_1-C_{15}) alkenyl, (C_1-C_{10}) alkenyl, (C_1-C_7) alkenyl) or

20 heteroalkyl);

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

22 wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

2 Particularly preferred derivatives of cytosine include those compounds of the
aforementioned structure (IV) wherein:

- 4 - R_1 and R_2 are the same or different and are hydrogen or acyl;
- R_3 is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-
6 ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl or
8 alkenyl;

 wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

10 wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl,
deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

12

 Particularly preferred embodiments of the aforementioned structure (IV) include

14 those derivatives of cytosine having R_1 , R_2 , R_3 , R_4 and R_5 as defined in Table 4:

Table 4 – Preferred Cytosine Derivatives

Structure	R ₁	R ₂	R ₃	R ₄	R ₅
(IV-a)	Acyl	H	H	H	H
(IV-b)	Acyl	H	Saccharide	H	H
(IV-c)	Acyl	Alkyl	H	H	H
(IV-d)	Acyl	Alkyl	Saccharide	H	H
(IV-e)	Acyl	H	H	H	Alkyl
(IV-f)	Acyl	H	H	Alkyl	Alkyl
(IV-g)	Heteroacyl	H	Saccharide	H	H
(IV-h)	Aryl	H	H	H	H
(IV-i)	Aryl	H	Saccharide	H	H
(IV-j)	Aryl	Alkyl	H	H	H
(IV-k)	Aryl	Alkyl	Saccharide	H	H
(IV-l)	Aryl	H	H	H	Alkyl
(IV-m)	Alkyl	H	H	H	H
(IV-n)	Alkyl	H	Saccharide	H	H
(IV-o)	Alkyl	Alkyl	H	H	H
(IV-p)	Alkyl	Alkyl	Saccharide	H	H
(IV-q)	Alkyl	H	H	H	Alkyl

2

Preferred embodiments of contemplated cytosine derivatives include acyl-cytidines

4 and acyl-cytosines. Particularly preferred embodiments of contemplated cytosine

derivatives are mono-acyl-cytidines and mono-acyl-cytosines. Preferred embodiments of

2 contemplated cytosine derivatives include heteroacyl-cytidines and heteroacyl-cytosines.

Preferred embodiments of contemplated cytosine derivatives include mono-heteroacyl-

4 cytidines and mono-heteroacyl-cytosines. Particularly preferred embodiments of

contemplated cytosine derivatives further include N4-acyl-cytidine and N4-acyl-cytosine.

6 Particularly preferred embodiments of contemplated cytosine derivatives further include N4-

heteroacyl-cytidine and N4-heteroacyl -cytosine. Especially preferred embodiments of

8 contemplated cytosine derivatives further include N4-acetyl-cytidine and N4-acetyl-

cytosine.

10 Additional preferred embodiments contemplated by the instant invention include

racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts

12 (including alternative salts, as well as pharmaceutically acceptable salts, including

alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives

14 of any of the aforementioned contemplated derivatives of cytosine described in this

subsection ("Cytosine Derivatives").

16

Purine and Pyrimidine Derivatives

18 Contemplated purine derivatives and pyrimidine derivatives include the purine

derivatives and pyrimidine derivatives set forth above in the structures (I), (II), (III) and

20 (IV). Additional examples of contemplated purine derivatives and/or pyrimidine

derivatives, which may include but are not limited to those compounds encompassed by the

22 structures (I), (II), (III) and (IV), are disclosed in one or more of the following references,

the entirety of each of which is herein incorporated by reference:

- 1) Sheikha et al., Nucleosides Nucleotides Nucleic Acids. 2002 Oct;21(10):619-35;
- 2 2) Muller et al., Chem Res Toxicol. 1998 May;11(5):454-63;
- 3) Dolan et al., Cancer Res. 1994 Oct 1;54(19):5123-30;
- 4 4) Hua et al., J Med Chem. 1987 Jan;30(1):198-200;
- 5) Melanoma Res. 2002 Oct;12(5):417-27;
- 6 6) Gu et al., Biochemistry. 2002 Jun 11;41(23):7508-18;
- 7) Buchdahl et al., Melanoma Res. 1998 Apr;8(2):123-30;
- 8 8) Debiton et al., Br J Cancer. 1997;76(9):1157-62;
- 9) Mounetou et al., J Med Chem. 1997 Aug 29;40(18):2902-9;
- 10 10) Cussac et al., J Pharmacol Exp Ther. 1994 Dec;271(3):1353-8;
- 11) Cussac et al., Drug Metab Dispos. 1994 Jul-Aug;22(4):637-42;
- 12 12) Bleasdale et al., Chem Res Toxicol. 1993 Jul-Aug;6(4):407-12;
- 13) Nukaya et al., Chem Pharm Bull (Tokyo). 1993 Apr;41(4):649-53;
- 14 14) Langlois et al., J Biol Stand. 1986 Jul;14(3):201-11;
- 15) Dutta et al., Biochemistry. 1975 Jul 15;14(14):3144-51;
- 16 16) Reese et al., J Chem Soc [Perkin 1]. 1972;23:2937-40;
- 17) Wang et al., J Org Chem. 2002 Nov 29;67(24):8507-12;
- 18 18) Kaiya et al., Nucleosides Nucleotides Nucleic Acids. 2002 Jun-Jul;21(6-7):427-33;
- 19) Muller et al., Chem Res Toxicol. 1998 May;11(5):454-63;
- 20 20) Francom et al., J Org Chem. 2003 Jan 24;68(2):666-9;
- 21) Garcia-Sastre et al., Biochem J. 1991 Jan 15;273(Pt 2):435-41;
- 22 22) Vaghefi et al., J Med Chem. 1987 Aug;30(8):1391-9;
- 23) Thomassen et al., Biochim Biophys Acta. 1983 Apr 22;723(1):114-22;

- 24) Watanabe et al., Eur J Biochem. 1981 Jul;117(3):553-8;
- 2 25) Watanabe et al., Nucleic Acids Symp Ser. 1979;(6):s79-82;
- 26) Dutta et al., Biochemistry. 1975 Jul 15;14(14):3144-51;
- 4 27) Rajabalee et al., Angew Chem Int Ed Engl. 1971 Jan;10(1):74;
- 28) Rao et al., J Am Chem Soc. 1970 Aug 12;92(16):4963-70;
- 6 29) Hall et al., Biochem Biophys Res Commun. 1970 Feb 6;38(3):496-9; and
- 30) Ingall et al., J. Med Chem., 1999, 42, 213-220.

8

Preferred embodiments of contemplated purine derivatives and pyrimidine

10 derivatives include acyl-cytidines, acyl-cytosines, acyl-adenosines, acyl-adenines, acyl-
guanosines, and acyl-guanines. Preferred embodiments of contemplated purine derivatives
12 and pyrimidine derivatives include heteroacyl-cytidines, heteroacyl-cytosines, heteroacyl-
adenosines, heteroacyl-adenines, heteroacyl-guanosines, and heteroacyl-guanines.

14 Particularly preferred embodiments of contemplated purine derivatives and pyrimidine
derivatives are mono-acyl-cytidines, mono-acyl-cytosines, mono-acyl-adenosines, mono-
16 acyl-adenines, mono-acyl-guanosines, and mono-acyl-guanines. Particularly preferred
embodiments of contemplated purine derivatives and pyrimidine derivatives are a mono-
18 heteroacyl-cytidine, a mono-heteroacyl-cytosine, a mono-heteroacyl-adenosine, a mono-
heteroacyl-adenine, a mono-heteroacyl-guanine, and a mono-heteroacyl-guanosine.

20 Particularly preferred embodiments of contemplated purine derivatives and
pyrimidine derivatives further include N6-gamma, gamma-dimethyl-allyl-aminopurine,
22 dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine,
N4-acetyl-cytidine, N4-acetyl-cytosine, N6-benzyl-adenine, N6-benzyl-adenosine, N6-

acetyl-adenine, N6-acetyl-adenosine, kinetin (6-furfurylaminopurine), kinetin riboside, N2-
2 acetyl-guanosine and N2-acetyl-guanine. N2-acyl-guanosine and N2-acyl-guanine
derivatives are especially preferred.

4 Additional non-limiting examples of contemplated purine derivatives and pyrimidine
derivatives, which may include but are not limited to those compounds encompassed by the
6 structures (I), (II), (III) and (IV), include one or more of the following purine derivatives and
pyrimidine derivatives: 1-methyladenosine; 2-methyladenosine; N6-methyladenosine; 2'-O-
8 methyladenosine; 2-methylthio-N6-methyladenosine; N6-isopentenyladenosine; 2-
methylthio-N6-isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-
10 N6-(cis-hydroxyisopentenyl) adenosine; N6-glycinylocarbamoyl-adenosine; N6-
threonylocarbamoyl-adenosine; 2-methylthio-N6-threonyl carbamoyl-adenosine; N6-methyl-
12 N6-threonylocarbamoyl-adenosine; N6-hydroxynorvalylcarbamoyl-adenosine; 2-methylthio-
N6-hydroxynorvalyl carbamoyl-adenosine, 2'-O-ribosyladenosine; 3-methylcytidine; 5-
14 methylcytidine; 2'-O-methylcytidine; 2-thiocytidine, N4-acetylcytidine; 5-formylcytidine;
5,2'-O-dimethylcytidine; N4-acetyl-2'-O-methylcytidine; 1-methylguanosine; N2-
16 methylguanosine; 7-methylguanosine; 2'-O-methylguanosine; N2,N2 dimethylguanosine;
N2,2'-O-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; 2'-O-ribosylguanosine; 7-
18 cyano-7-deazaguanosine; 7-aminomethyl-7-deazaguanosine; N6,N6-dimethyladenosine; 2'-
O-methylinosine; N4-methylcytidine; N4,2'-O-dimethylcytidine ; N6,2'-O-
20 dimethyladenosine; N6,N6,O-2'-trimethyladenosine; N2 ,7-dimethylguanosine; N2 ,N2 ,7-
trimethylguanosine; and 5-formyl-2'-O-methylcytidine.

22 Additional non-limiting examples of contemplated compounds, which may include
but are not limited to those compounds encompassed by the structures (I), (II), (III) and

(IV), include the purine derivatives and pyrimidine derivatives disclosed in the following
2 patents and published patent applications, each of which is herein incorporated by reference:
US Patent 3,988,338; US Patent 4,581,056; US Patent 5,075,445; US Patent 5,412,088; US
4 Patent 4,199,574; US Patent 4,748,177; EP 0 224 722 A1; US Patent 5,057,517; EP 1 258
247 A1; WO 02/092093 A1; US Patent 6,294,522; Published US Application
6 2002/0045595A1; US Patent 6,258,793; Published US Application 2002/0037872A1; EP 1
054 012 A1; EP 1 300 147 A1; US Patent 6,348,451; US Patent 6,525,083; WO 01/40246
8 A1; US Patent 6,316,426; Published US Application 2002/0035086A1; US Patent
5,066,655; US Patent 5,565,565; US Patent 5,565,566; US Patent 6,429,315; US Patent
10 6,344,447; WO 00/40584 A1; WO 01/40246 A1; and WO 91/13082 A1.

Additional contemplated compounds of the instant invention include racemates,
12 enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including
alternative salts, as well as pharmaceutically acceptable salts, including alternative
14 pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any one
or more the compounds described in this section (Section B: "Compounds of the Invention")
16 of the instant application. Among the contemplated compounds are activators of AMPK
and/or Akt.

18 Preferred acyl substituent groups on a hydroxyl group, including one or more
hydroxyl groups of a saccharide moiety when present, are fatty acids with 6 to 16 carbon
20 atoms, or dicarboxylic acids with 4 to 6 carbon atoms, e.g., succinic, glutaric, or adipic
acids. Preferred substituents on an amine group, especially an exocyclic amine group,
22 include amino acids with basic side chains, e.g., lysine or arginine. Other preferred
substituents on an amine include acetic acid, nicotinic acid and para-aminobenzoic acid.

Contemplated derivatives of purines and pyrimidines may be synthesized by
2 methods well known in the art. Non-limiting examples of such known methods are
disclosed in the following patents and published patent applications, each of which is herein
4 incorporated by reference: US Patent 5,075,445; US Patent 5,412,088; US Patent
4,199,574; US Patent 4,748,177; EP 0 224 722 A1; US Patent 5,057,517; EP 1 258 247 A1;
6 WO 02/092093 A1; US Patent 6,294,522; Published US Application 2002/0045595A1; US
Patent 6,258,793; Published US Application 2002/0037872A1; EP 1 054 012 A1; EP 1 300
8 147 A1; US Patent 6,348,451; US Patent 6,525,083; WO 01/40246 A1; US Patent
6,316,426; Published US Application 2002/0035086A1; US Patent 5,066,655; US Patent
10 5,565,565; US Patent 5,565,566; US Patent 6,429,315; US Patent 6,344,447; WO 00/40584
A1; WO 01/40246 A1; WO 91/13082 A1. Additionally, the synthesis of N-Acetyl-3',5'-di-
12 O-acetyl-2'-deoxyadenosine has been described by M.J. Robins and R.K. Robins in
Interscience Publishers, 1968, pp 519-520 (edited by W.W. Zorbach and R.S. Tipson), the
14 entirety of which is herein incorporated by reference; the synthesis of acyl-cytosines has
been described by D. M. Brown, A. Todd and S. Varadarajan in J. Chem. Sc., pp 2384-2387,
16 1956, the entirety of which is herein incorporated by reference; the synthesis of N-acetyl-
2'-deoxycytidine has been described in Synthetic Procedures in Nucleic Acid Chemistry,
18 edited by W.W. Zorbach and R.S. Tipson, Interscience Publishers, 1968, p.285-287, the
entirety of which is herein incorporated by reference; the synthesis of N-4-Acetyl cytosine
20 nucleosides has been described by M. Ariatti and P.A. Jones, Biochemistry International,
15(6), pp.1097-1103 (1987), the entirety of which is herein incorporated by reference; and
22 the synthesis of N-4-acetyl-cytidine has been described by K.A. Watanabe and J.J. Fox in

Angew. Chem. Internat.Edit. 5(6), pp 579-580 (1966), the entirety of which is herein

2 incorporated by reference.

Well-known methods for synthesizing acylated derivatives of purines and
4 pyrimidines include reacting a purine or a pyrimidine, or a congener of either, with an
activated carboxylic acid, such as a carboxylic acid that has been treated with appropriate
6 reagents to render its carboxylate carbon more susceptible to nucleophilic attack than is the
case in the original carboxylic acid. Well known examples of useful activated carboxylic
8 acids for synthesis of the compounds of the invention are acid chlorides, acid anhydrides, n-
hydroxysuccinimide esters, or carboxylic acids activated with BOP-DC. Carboxylic acids
10 may also be linked to a purine or a pyrimidine, or a congener of either, with coupling
reagents like dicyclohexylcarbodiimide (DCC).

12 During preparation of the acyl compounds contemplated by the invention, when the
acid source of the desired acyl derivative has groups which interfere with the acylation
14 reactions, e.g., hydroxyl or amino groups, these groups may be blocked with protecting
groups, e.g., t-butyldimethylsilyl ethers or t-BOC groups, respectively, before preparation of
16 the anhydride. For example, lactic acid may be converted to 2-t-
butyldimethylsiloxypropionic acid with t-butyldimethylchlorosilane, followed by hydrolysis
18 of the resulting silyl ester with aqueous base. The anhydride may be formed by reacting the
protected acid with DCC. With amino acids, the N-t-BOC derivative may be prepared using
20 standard techniques, which derivative may then converted to the anhydride with DCC. With
acids containing more than one carboxylate group (e.g., succinic, fumaric, or adipic acid) the
22 acid anhydride of the desired dicarboxylic acid may be, for example, reacted with a purine
or pyrimidine in pyridine or pyridine plus dimethylformamide or dimethylacetamide.

Amino acids may be coupled to the exocyclic amino groups, such as those of
2 cytidine, and to hydroxyl groups, such as those on the aldose moiety of nucleosides or their
congeners, using DCC in a suitable solvent, particularly a mixture of (i) methylene chloride
4 and (ii) dimethylacetamide or dimethylformamide, for example.

Carbyloxycarbonyl derivatives of a purine or pyrimidine, or a congener of either,
6 may be prepared by reacting with the appropriate carbylchloroformate in a solvent such as
pyridine or pyridine plus dimethylformamide under anhydrous conditions, for example. The
8 solvent may be removed under vacuum, and the residue purified by column
chromatography.

10 In still further alternative aspects, it should be appreciated that certain of the
contemplated compounds, in addition to being synthesized in vitro, may also be isolated
12 from natural sources. Preferred natural sources include *Hordeum vulgare* or malted seed
therefrom. Other preferred natural sources include *Hordeum sativum*, *Hordeum jubatum*,
14 *Hordeum murinum*, or malted seed therefrom. Contemplated compounds also include
purine derivatives and pyrimidine derivatives, in substantially pure form, obtainable through
16 purification from natural sources. Particularly preferred natural sources include malted
barley seed extracts and brewer's yeast extracts.

18 Among preferred naturally occurring derivatives contemplated by the invention are
the cytokinins. Plants are particularly rich sources of various cytokinins, with *Hordeum*
20 *vulgare*, or malted seed therefrom, being a particularly preferred source for obtaining
various cytokinins. Other preferred natural sources include *Hordeum sativum*, *Hordeum*
22 *jubatum*, *Hordeum murinum*, or malted seed therefrom. Especially preferred sources from
which such substantially pure compounds may be purified include the malted barley seed

extracts disclosed in WO 01/66146 A1, WO 02/072148 A1, and U.S. Provisional Patent
2 Application 60/408,887, the entireties of which are herein incorporated by reference.
Consequently, it should be appreciated that contemplated compounds may be entirely or
4 partially synthesized/modified. For example, where contemplated compounds are partially
synthesized, a precursor of contemplated compounds may be isolated from a plant or
6 microorganism, and then subjected to one or more steps to arrive at a contemplated
compound. Contemplated compounds may be modified in one or more synthetic steps to
8 impart a particularly desirable physico-chemical property. For example, contemplated
compounds may be esterified with a polar compound (*e.g.*, polyethylene glycol) to increase
10 water solubility. In another example, contemplated compounds may be coupled to a resin or
other material to control the rate of release to the organism.

12 The forgoing are illustrative, and not limiting, examples of methods and sources that
can be used to prepare and/or obtain the contemplated compounds and compositions of the
14 present invention. Thus, it will be understood to the person skilled in the art that other
methods and sources can be used to prepare and/or obtain the contemplated compounds and
16 compositions of the invention.

18 **C. Assay and Screening Methods of the Invention**

Among the embodiments of the instant invention are methods for determining the
20 degree to which a candidate compound activates adenosine monophosphate activated protein
kinase (AMPK), such methods comprising: 1) contacting cells or tissues expressing
22 AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate
compound; and 2) measuring an indicator of AMPK activity to determine the degree to

which the candidate compound activates AMPK; wherein the candidate compound is a
2 cytokinin of structure (I), an adenine derivative of structure (II), a guanine derivative of
structure (III), and/or a cytosine derivative of structure (IV). In a preferred embodiment of
4 such a method, the candidate compound is selected from a group of candidate compounds,
the group of candidate compounds comprising two or more different cytokinins of structure
6 (I), two or more different adenine derivatives of structure (II), two or more different
guanine derivatives of structure (III) or two or more different cytosine derivatives of
8 structure (IV). In a preferred embodiment, measuring an indicator of AMPK activity to
determine the degree to which the candidate compound activates AMPK results in a test
10 value being determined, where the test value is compared with a corresponding control
value, which as would be readily apparent to one of skill in the art, is a value determined
12 under the same or similar conditions as the test value, but in the absence of, or in the
presence of a reduced concentration of, the candidate compound.

14 As would be apparent to one of skill in the art, such methods for determining the
degree to which a candidate compound activates AMPK in certain cell types and/or tissue
16 types find utility in assessing the potential of certain compounds of the invention as drugs
useful in treating a variety of disorders that are ameliorated through activation of AMPK in
18 certain cell types and/or tissue types, such as those disorders well known in the art and/or
exemplified in the instant application. The contemplated methods are also suitable for use
20 in screening methods for identifying drugs useful in treating a variety of disorders that are
ameliorated through activation of AMPK in certain cell types and/or tissue types, such as
22 those disorders well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of
2 AMPK activity to determine the degree to which AMPK is activated under test conditions,
and many such methods are well-known. For example, see WO 00/28076 A1, WO
4 02/09726 A1 and WO 03/037371 A2, the entireties of which are herein incorporated by
reference. Such methods include:

6 1. AMPK has been found to be a heterotrimeric complex composed of a catalytic
subunit (alpha) and two regulatory subunits (beta and gamma). Activation of AMPK leads to
8 phosphorylation of the catalytic unit (the alpha unit) on a given residue (Thr 172) that can be
identified using specific antibodies reacting with the phosphorylated form of the AMPK
10 alpha unit. Briefly, the ability of a given compound or procedure to activate the AMPK can
be evaluated by its ability to induce phosphorylation of the Thr 172 residues on the AMPK
12 catalytic subunit. (For a recent example, see Fryer LG, Parbu-Patel and Carling, J. Biol.
Chem 2002 277:25226 the entirety of which are herein incorporated by reference.)

14 2. Further, activation of AMPK is well-known to increase glucose uptake in several
cell lines and tissues. Upon activation, AMPK induces glucose uptake that can be monitored
16 using a radioactive ligand (glucose or glucose mimetic). Briefly, the ability of a given
compound or procedure to activate the AMPK can be evaluated by its ability to increase
18 glucose uptake in a given cell line or tissue. (See Abbud W, Habinowski S, Zhang JZ,
Kendrew J, Elkairi FS, Kemp BE, Witters LA, Ismail-Beigi F, Arch Biochem Biophys 2000
20 380:347, the entirety of which are herein incorporated by reference.)

3. Evaluation of the ability of AMPK, a serine/threonine protein kinase, to
22 phosphorylate *in vivo* or *in vitro* a given substrate. Typically, in these experiments the
substrate is a protein or a peptide containing a sequence similar to the sequence surrounding

the site phosphorylated by AMPK on its natural substrates. The AMARA peptide
2 (AMARAASAAALARRR) and the SAMS peptide (HMRSAMSGHLVKRR) are typically
used as substrates in these studies. Briefly, AMPK-containing cell extracts or purified
4 forms of the AMPK are incubated in the presence of a substrate, an adequate reaction mix
and a tracer, usually a phosphorylated form of ATP. (For an example, see Davies et al., S.
6 P., Carling, D. and Hardie, D. G. (1989) Eur. J. Biochem. 186. 123-128, the entirety of
which are herein incorporated by reference.) More recently, eNOS, nNOS and nNOS μ have
8 been proposed as substrates for assessing AMPK activity the presence of putative AMPK
activators. (For example, see WO 00/28076 A1) In the case of eNOS, phosphorylation of
10 threonine 495 in the presence of limiting calcium has been suggested as a measure to be
assessed, and in the case of nNOS and nNOS μ , phosphorylation of Serine-1417 is suggested
12 as a measure to be assessed.

As one of skill in the art would recognize, a wide a variety of cell types and/or tissue
14 types that express AMPK, or that are capable of expressing AMPK, may be employed in the
methods of the invention. Preferred cell types and/or tissue types include one or more of
16 myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue,
pancreatic cells, pancreatic tissue, adipocytes and adipose tissue. Other preferred cell types
18 include one or more of 3T3-L1 cells, Chinese Hamster Ovary cells, C2C12 cells and L6
cells. Especially preferred cell lines for Western immunoblotting include the C2C12 mouse
20 muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells
(from Clonetics, Inc.)

22 Among the embodiments of the instant invention are methods for determining the
degree to which a candidate compound activates Akt, where such methods comprise: 1)

contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts
2 therefrom, with the candidate compound; and 2) measuring an indicator of Akt activity to
determine the degree to which the candidate compound activates Akt; wherein the candidate
4 compound is a cytokinin of structure (I), an adenine derivative of structure (II), a guanine
derivative of structure (III), and/or a cytosine derivative of structure (IV). In a preferred
6 embodiment of such a method, the candidate compound is selected from a group of
candidate compounds, the group of candidate compounds comprising two or more different
8 cytokinins of structure (I), two or more different adenine derivatives of structure (II), two or
more different guanine derivatives of structure (III) or two or more different cytosine
10 derivatives of structure (IV). In a preferred embodiment, measuring an indicator of Akt
activity to determine the degree to which the candidate compound activates Akt results in a
12 test value being determined, where the test value is compared with a corresponding control
value, which as would be readily apparent to one of skill in the art, is a value determined
14 under the same or similar conditions as the test value, but in the absence of, or in the
presence of a reduced concentration of, the candidate compound.

16 As would be apparent to one of skill in the art, such methods for determining the
degree to which a candidate compound activates Akt in certain cell types and/or tissue types
18 find utility in assessing the potential of certain compounds of the invention as drugs useful
in treating a variety of disorders that are ameliorated through activation of Akt in certain cell
20 types and/or tissue types, such as those disorders well known in the art and/or exemplified in
the instant application. The contemplated methods are also suitable for use in screening
22 methods for identifying drugs useful in treating a variety of disorders that are ameliorated

through activation of Akt in certain cell types and/or tissue types, such as those disorders
2 well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of Akt
4 activity to determine the degree to which Akt is activated under test conditions, and many
such methods are well-known. In general, such methods are analogous to the above
6 described methods that rely on measuring an indicator of AMPK activity for determining the
degree to which the candidate compound activates AMPK. For example, measuring the
8 phosphorylation of the serine 473 residue of Akt is a method that is well within the skill of
the art, and well-known, for measuring an indicator of Akt activity for determining the
10 degree to which Akt is activated under test conditions. As one of skill in the art would
recognize, a wide variety of cell types and/or tissue types that express Akt, or that are
12 capable of expressing Akt, may be employed in the methods of the invention. Preferred cell
types and/or tissue types include one or more of myocytes, fibroblasts, skeletal muscle cells,
14 skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes
and adipose tissue. Other preferred cell types include one or more of 3T3-L1 cells, Chinese
16 Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell lines for Western
immunoblotting include the C2C12 mouse muscle cells (from ATTC) as well as in primary
18 culture of human skeletal muscle cells (from Clonetics, Inc.)

Among the embodiments of the instant invention are methods for determining the
20 degree to which a candidate compound increases Glut-4 content of a cell, the method
comprising: 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-
22 4, or cellular extracts therefrom, with the candidate compound; and 2) measuring an
indicator of Glut-4 content to determine the degree to which the candidate compound

increases Glut-4 content; wherein the candidate compound is a cytokinin of structure (I), an
2 adenine derivative of structure (II), a guanine derivative of structure (III), and/or a cytosine
derivative of structure (IV). In a preferred embodiment of such a method, the candidate
4 compound is selected from a group of candidate compounds, the group of candidate
compounds comprising two or more different cytokinins of structure (I), two or more
6 different adenine derivatives of structure (II), two or more different guanine derivatives of
structure (III) or two or more different cytosine derivatives of structure (IV). In a preferred
8 embodiment, measuring an indicator of Glut-4 content to determine the degree to which the
candidate compound increases Glut-4 content results in a test value being determined, where
10 the test value is compared with a corresponding control value, which as would be readily
apparent to one of skill in the art, is a value determined under the same or similar conditions
12 as the test value, but in the absence of, or in the presence of a reduced concentration of, the
candidate compound.

14 As would be apparent to one of skill in the art, such methods for determining the
degree to which a candidate compound increases Glut-4 content in certain cell types and/or
16 tissue types find utility in assessing the potential of certain compounds of the invention as
drugs useful in treating a variety of disorders that are ameliorated through increasing Glut-4
18 content in certain cell types and/or tissue types, such as those disorders well known in the art
and/or exemplified in the instant application. The contemplated methods are also suitable
20 for use in screening methods for identifying drugs useful in treating a variety of disorders
that are ameliorated through increasing Glut-4 content in certain cell types and/or tissue
22 types, such as those disorders well known in the art and/or exemplified in the instant
application.

Various methods are well within the skill of the art for measuring an indicator of
2 Glut-4 content to determine the degree to which Glut-4 is activated under test conditions,
and many such methods are well-known. For example, antibodies raised against Glut-4 are
4 readily available for measuring Glut-4 content by Western immunoblotting. The use of such
antibodies in Western immunoblotting assays is well within the skill of the art, and well-
6 known, for measuring an indicator of Glut-4 content for determining the degree to which the
candidate compound increases Glut-4 content under test conditions. As one of skill in the
8 art would recognize, a wide variety of cell types and/or tissue types that express Glut-4, or
that are capable of expressing Glut-4, may be employed in the methods of the invention.
10 Preferred cell types and/or tissue types include one or more of myocytes, fibroblasts, skeletal
muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic
12 tissue, adipocytes and adipose tissue. Other preferred cell types include one or more of 3T3-
LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell
14 lines for Western immunoblotting include the C2C12 mouse muscle cells (from ATTC) as
well as in primary culture of human skeletal muscle cells (from Clonetics, Inc.)

16 Among the embodiments of the instant invention are methods for determining the
degree to which a candidate compound enhances translocation of Glut-4 from an
18 intracellular location to the plasma membrane of a cell, the method comprising: 1)
contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular
20 extracts therefrom, with the candidate compound; and 2) measuring an indicator of Glut-4
translocation to determine the degree to which the candidate compound enhances
22 translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;
wherein the candidate compound is a cytokinin of structure (I), an adenine derivative of

structure (II), a guanine derivative of structure (III), and/or a cytosine derivative of structure
2 (IV). In a preferred embodiment of such a method, the candidate compound is selected from
a group of candidate compounds, the group of candidate compounds comprising two or
4 more different cytokinins of structure (I), two or more different adenine derivatives of
structure (II), two or more different guanine derivatives of structure (III) or two or more
6 different cytosine derivatives of structure (IV). In a preferred embodiment, measuring an
indicator of Glut-4 translocation to determine the degree to which the candidate compound
8 enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a
cell results in a test value being determined, where the test value is compared with a
10 corresponding control value, which as would be readily apparent to one of skill in the art, is
a value determined under the same or similar conditions as the test value, but in the absence
12 of, or in the presence of a reduced concentration of, the candidate compound.

As would be apparent to one of skill in the art, such methods for determining the
14 degree to which a candidate compound enhances translocation of Glut-4 from an
intracellular location to the plasma membrane of a cell in certain cell types and/or tissue
16 types find utility in assessing the potential of certain compounds of the invention as drugs
useful in treating a variety of disorders that are ameliorated through enhancing translocation
18 of Glut-4 from an intracellular location to the plasma membrane of a cell in certain cell
types and/or tissue types, such as those disorders well known in the art and/or exemplified in
20 the instant application. The contemplated methods are also suitable for use in screening
methods for identifying drugs useful in treating a variety of such disorders that are
22 ameliorated through enhancing translocation of Glut-4 from an intracellular location to the

plasma membrane of a cell in certain cell types and/or tissue types, such as those disorders
2 well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of
4 Glut-4 translocation to determine the degree to which translocation of Glut-4 from an
intracellular location to the plasma membrane of a cell is enhanced under test conditions,
6 and many of such methods are well-known. For example, see US 6,303,373, the entirety of
which is herein incorporated by reference, for a representative disclosure of a method for
8 measuring an indicator of Glut-4 translocation to determine the degree to which
translocation of Glut-4 from an intracellular location to the plasma membrane of a cell is
10 enhanced under test conditions. As one of skill in the art would recognize, a wide variety of
cell types and/or tissue types that express Glut-4, or that are capable of expressing Glut-4,
12 may be employed in the methods of the invention. Preferred cell types and/or tissue types
include one or more of myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue,
14 liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
Other preferred cell types include one or more of 3T3-LI cells, Chinese Hamster Ovary
16 cells, C2C12 cells and L6 cells. Especially preferred cell lines for include the C2C12 mouse
muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells
18 (from Clonetics, Inc.)

D. Pharmaceutical Compositions and Dietary Supplements of the Invention

2 In another aspect, a preferred embodiment of the present invention provides a
pharmaceutical and/or nutraceutical that comprises a therapeutically effective amount of one
4 or more of the contemplated compounds of Section B ("Compounds of the Invention")
formulated together with one or more pharmaceutically acceptable carriers, including
6 additives and/or excipients and/or diluents.

As described in detail herein, the pharmaceutical compositions of the present
8 invention may be specially formulated for administration in solid or liquid form, including
preferred embodiments adapted for the following: (1) oral administration, for example,
10 drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders,
granules, pastes for application to the tongue; (2) parenteral administration, for example, by
12 subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or
suspension; or (3) topical application, for example, as a cream, ointment or spray applied to
14 the skin.

Formulations of the present invention include those suitable for oral, nasal, topical
16 (including buccal and sublingual) and/or parenteral administration. The formulations may
conveniently be presented in unit dosage form and may be prepared by any methods well
18 known in the art of pharmacy. The amount of active ingredient which can be combined with
a carrier material to produce a single dosage form will vary depending upon the host being
20 treated, the particular mode of administration. The amount of active ingredient which can be
combined with a carrier material to produce a single dosage form will generally be that
22 amount of the compound which produces a therapeutic effect. Generally, out of one hundred
per cent of the weight of a single dosage form, active ingredient will range from about 0.01

per cent to about ninety-nine percent of the total weight, more preferably from about 0.05
2 per cent to about 90 per cent, more preferably from about 0.1 per cent to about 90 per cent,
more preferably from about 0.5 per cent to about 85 per cent, more preferably from about 1
4 per cent to about 80 per cent, more preferably from about 5 per cent to about 70 per cent,
most preferably from about 10 per cent to about 30 per cent. In preferred embodiments, the
6 weight of active ingredient will constitute at least a certain percentage of the total weight of
the single dosage form, the certain percentage being selected from one or more of the
8 following: about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about
3%, about 4%, about 5%, about 7.5%, about 10%, about 20%, about 30%, about 40%, about
10 50%, about 60%, about 70%, about 80%, about 90%, about 95% or about 99%. In certain
preferred embodiments, the weight of active ingredient will constitute no more than a certain
12 percentage of the total weight of the single dosage form, the certain percentage being
selected from one or more of the following: about 0.01%, about 0.05%, about 0.1%, about
14 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%, about 7.5%, about 10%, about
20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%,
16 about 95% or about 99%.

Methods of preparing these formulations or compositions include the step of
18 bringing into association a contemplated compound (or compounds) of the present invention
with the carrier and/or one or more accessory ingredients. In preferred embodiments, the
20 contemplated compound is substantially pure prior to being brought into association with the
carrier and/or one or more accessory ingredients.

In general, the formulations are prepared by uniformly and intimately bringing into
2 association a contemplated compound of the present invention with liquid carriers, or finely
divided solid carriers, or both, and then, if necessary, shaping the product.

4 An oral route of administration is preferred for the pharmaceuticals, including
nutraceuticals, of the invention. Formulations of the invention suitable for oral
6 administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a
flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution
8 or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil
liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin
10 and glycerin, or sucrose and acacia) and/or as bronchoalveolar lavages for intended delivery
systems to the lung and the like, each containing a predetermined amount of a compound of
12 the present invention as an active ingredient. A compound of the present invention may also
be administered as a bolus, electuary or paste.

14 In a preferred embodiments to prepare an orally administerable solid dosage form
(e.g. capsules, tablets, pills, dragees, powders, granules and the like), an active ingredient is
16 mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or
dicalcium phosphate, and/or any other pharmaceutically acceptable carriers such as: (1)
18 fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid;
(2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl
20 pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating
agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain
22 silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6)
absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such

as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and
2 bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid
polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) coloring agents: (11)
4 phosphate-buffered saline solution (12) emulsions, such as an oil/water or water/oil
emulsion; (12) adjuvants; and (13) sterile aqueous solutions, for example. In the case of
6 capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering
agents. Solid compositions of a similar type may also be employed as fillers in soft and
8 hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high
molecular weight polyethylene glycols and the like.

10 A tablet may be made by compression or molding, optionally with one or more
accessory ingredients. Compressed tablets may be prepared using binder (for example,
12 gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant
(for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose),
14 surface-active or dispersing agent. Molded tablets may be made by molding in a suitable
machine a mixture of the powdered compound moistened with an inert liquid diluent.

16 The tablets and other solid dosage forms of the pharmaceutical compositions of the
present invention, such as dragees, capsules, pills and granules, may optionally be scored or
18 prepared with coatings and shells, such as enteric coatings and other coatings well known in
the pharmaceutical-formulating art. They may also be formulated so as to provide slow or
20 controlled release of the active ingredient therein using, for example, hydroxypropylmethyl
cellulose in varying proportions to provide the desired release profile, other polymer
22 matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration
through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile

solid compositions which can be dissolved in sterile water, or some other sterile injectable
2 medium immediately before use. These compositions may also optionally contain
opacifying agents and may be of a composition that they release the active ingredient(s)
4 only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a
delayed manner. Examples of embedding compositions which can be used include
6 polymeric substances and waxes. The active ingredient can also be in micro-encapsulated
form, if appropriate, with one or more of the above-described excipients.

8 Liquid dosage forms for oral administration of the compounds of the invention
include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions,
10 syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain
inert diluents commonly used in the art, such as, for example, water or other solvents,
12 solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate,
ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in
14 particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol,
tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures
16 thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as
18 wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring,
perfuming and preservative agents.

20 Suspensions, in addition to the active compounds, may contain suspending agents as,
for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,
22 microcrystalline cellulose, aluminum metahydroxide, bentonite, agar--agar and tragacanth,
and mixtures thereof.

The ointments, pastes, creams and gels may contain, in addition to an active
2 compound of this invention, excipients, such as animal and vegetable fats, oils, waxes,
paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones,
4 bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Pharmaceutical compositions of this invention suitable for parenteral administration
6 comprise one or more compounds of the invention in combination with one or more
pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions,
8 suspensions or emulsions, or sterile powders which may be reconstituted into sterile
injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers,
10 solutes which render the formulation isotonic with the blood of the intended recipient or
suspending or thickening agents.

12 Examples of suitable aqueous and non-aqueous carriers which may be employed in
the pharmaceutical compositions of the invention include water, ethanol, polyols (such as
14 glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof,
vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper
16 fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by
the maintenance of the required particle size in the case of dispersions, and by the use of
18 surfactants.

These compositions may also contain adjuvants such as preservatives, wetting
20 agents, emulsifying agents and dispersing agents. Prevention of the action of
microorganisms may be ensured by the inclusion of various antibacterial and antifungal
22 agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be
desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the

compositions. In addition, prolonged absorption of the injectable pharmaceutical form may
2 be brought about by the inclusion of agents which delay absorption such as aluminum
monostearate and gelatin.

4 In some cases, in order to prolong the effect of a drug, it is desirable to slow the
absorption of the drug from subcutaneous or intramuscular injection. This may be
6 accomplished by the use of a liquid suspension of crystalline or amorphous material having
poor water solubility. The rate of absorption of the drug then depends upon its rate of
8 dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively,
delayed absorption of a parenterally-administered drug form is accomplished by dissolving
10 or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject
12 compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the
ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug
14 release can be controlled. Examples of other biodegradable polymers include
poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by
16 entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered to humans or other
18 animals, they can be given *per se* or as a pharmaceutical composition comprising the active
ingredient(s) and a pharmaceutically acceptable carrier. In preferred embodiments, the
20 active ingredient or ingredients represent, in total, about 0.01 to about 99.5% by weight
(more preferably, about 0.5 to about 90% by weight) of the total formulation, for example.
22 In particularly preferred embodiments, the active ingredient represents at least about 0.01%,
about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%,

about 7.5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about
2 70%, about 80%, about 90%, about 95% or about 99% by weight of the pharmaceutical
composition.

4 The preparations of the present invention may be given by routes including oral,
parenteral, and topical routes. They are of course given by forms suitable for each
6 administration route. Oral administration is preferred. And the preferred form for oral
administration is tablet or capsule.

8 Regardless of the route of administration selected, the compounds of the present
invention, which may be used in a suitable hydrated form, and/or the pharmaceutical
10 compositions of the present invention, are formulated into pharmaceutically acceptable
dosage forms by conventional methods known to those of skill in the art.

12 Actual dosage levels of the active ingredients in the pharmaceutical compositions of
this invention may be varied so as to obtain an amount of the active ingredient which is
14 effective to achieve the desired therapeutic response for a particular patient, composition,
and mode of administration, without being toxic to the patient.

16 The selected dosage level will depend upon a variety of factors including the activity
of the particular compound of the present invention employed, or the ester, salt or amide
18 thereof, the route of administration, the time of administration, the rate of excretion of the
particular compound being employed, the duration of the treatment, other drugs, compounds
20 and/or materials used in combination with the particular compound employed, the age, sex,
weight, condition, general health and prior medical history of the patient being treated, and
22 like factors well known in the medical arts.

2 A physician or veterinarian having ordinary skill in the art can readily determine and
prescribe the effective amount of the pharmaceutical composition required. For example, the
physician or veterinarian could start doses of the compounds of the invention employed in
4 the pharmaceutical composition at levels lower than that required in order to achieve the
desired therapeutic effect and gradually increase the dosage until the desired effect is
6 achieved.

In general, a suitable daily dose of a compound of the invention will be that amount
8 of the compound which is the lowest dose effective to produce a therapeutic effect. Such an
effective dose will generally depend upon the factors described above. Generally, doses of
the compounds of this invention for a patient, when used for the indicated effects, will range
10 from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably
from about 0.01 to about 50 mg per kg per day, and still more preferably from about 0.1 to
12 about 40 mg per kg per day.

14 In preferred embodiments, a unit dose of the compound of this invention for a
patient, when used for the indicated effects, will range from about 0.001 mg to about 1000
mg, more preferably from about 0.01 mg to about 500 mg, still more preferably from about
0.01 mg to about 100 mg, still more preferably from about 0.01 mg to about 10 mg, still
18 more preferably from about 0.01 mg to about 1 mg. In preferred embodiments, a unit dose
of the compound of this invention for a patient, when used for the indicated effects, will
20 range from about from about 0.1 mg to about 10 mg. In preferred embodiments, a unit dose
of the compound of this invention for a patient, when used for the indicated effects, will
22 range from about from about 0.1 mg to about 1 mg. In preferred embodiments, a unit dose
of the compound of this invention for a patient, when used for the indicated effects, will

range from about from about 1 mg to about 10 mg. In preferred embodiments, a unit dose of
2 the compound of this invention for a patient, when used for the indicated effects, will range
from about from about 10 mg to about 25 mg. In preferred embodiments, a unit dose of the
4 compound of this invention for a patient, when used for the indicated effects, will range
from about from about 25 mg to about 50 mg. In preferred embodiments, a unit dose of the
6 compound of this invention for a patient, when used for the indicated effects, will range
from about from about 50 mg to about 100 mg. In preferred embodiments, a unit dose of
8 the compound of this invention for a patient, when used for the indicated effects, will be
selected from one or more of about 0.001 mg, about 0.01 mg, about 0.1 mg, about 0.25
10 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, about 2.5 mg, about 5 mg,
about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 50 mg, about 100 mg, about
12 200 mg, about 500 mg and about 1,000 mg.

In preferred embodiments, a unit dose of the compound of this invention for a
14 patient, when used for the indicated effects, will be selected from amount sufficient to
increase, following oral or parenteral administration of said unit dosage to a patient in need
16 thereof, an intracellular level of activated AMPK and/or an intracellular level of activated
Akt in one or more cell types and/or tissue types of said patient. In especially preferred
18 embodiments, a unit dose of the compound of this invention for a patient, when used for the
indicated effects, will be selected from an amount sufficient to increase the intracellular
20 level of activated AMPK and/or the intracellular level of activated Akt in one or more cell
types and/or tissue types of said patient by at least about 20% over pre-administration levels.
22 In other preferred embodiments, a unit dose of the compound of this invention for a patient,
when used for the indicated effects, will be selected from an amount sufficient to increase,

over pre-administration levels, the intracellular level of activated AMPK and/or the
2 intracellular level of activated Akt in one or more cell types and/or tissue types of said
patient by at least about 30%, at least about 50%, at least about 75%, at least about two-fold,
4 at least about four-fold, or at least about ten-fold. In other preferred embodiments, a unit
dose of the compound of this invention for a patient, when used for the indicated effects,
6 will be selected from an amount sufficient to increase, over pre-administration levels, the
intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or
8 more cell types and/or tissue types of said patient by up to about 30%, up to about 50%, up
to about 75%, up to about two-fold, up to about four-fold, up to about ten-fold or up to about
10 fifteen-fold.

If desired, the effective daily dose of the active compound may be administered as
12 two, three, four, five, six or more sub-doses administered separately at appropriate intervals
throughout the day, optionally, in unit dosage forms.

14 While it is possible for a compound of the present invention to be administered
alone, it is preferable to administer the compound as a pharmaceutical composition, where
16 the pharmaceutical composition comprises, or preferably consists essentially of, one or
contemplated compounds, a pharmaceutically acceptable carrier, and optionally, one or
18 more additional therapeutic ingredients. It is especially preferred that a compound of the
invention be administered in the form of a substantially pure pharmaceutical composition.

20 The pharmaceutical compositions of the instant invention comprise one or more of
the contemplated purine derivatives, including cytokinins, adenine derivatives, and guanine
22 derivatives, and/or one or more pyrimidine derivatives, including cytosine derivatives, as
disclosed in Section B ("Compounds of the Invention") of the instant application.

Cytokinins, adenine derivatives, guanine derivatives, and cytosine derivatives preferred for
2 use in the pharmaceutical compositions of the instant invention include those set forth in the
aforementioned structures (I), (II), (III) and (IV), respectively, as well as racemates,
4 enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including
alternative salts, as well as pharmaceutically acceptable salts, including alternative
6 pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives thereof.
Contemplated compounds that are preferred for use in the pharmaceutical compositions of
8 the instant invention include a mono-acyl-cytosine, a mono-acyl-adenine, a mono-acyl-
adenosine, a mono-acyl-guanosine, and a mono-acyl-guanine, as well as racemates,
10 enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including
alternative salts, as well as pharmaceutically acceptable salts, including alternative
12 pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives thereof,
where the contemplated compound is an activator of AMPK and/or Akt. Particularly
14 preferred purine derivatives and pyrimidine derivatives that are activators of AMPK and/or
Akt, and that are preferred for use in the pharmaceutical compositions of the instant
16 invention, further include N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin,
cis-zeatin; trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N4-acetyl-
18 cytidine, N4-acetyl-cytosine, N6-benzyl-adenine, N6-benzyl-adenosine, N6-acetyl-adenine,
N6-acetyl-adenosine, kinetin riboside, kinetin, N2-acetyl-guanosine and N2-acetyl-guanine.
20 N2-acyl-guanosine and N2-acyl-guanine derivatives are especially preferred; as well as
racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts
22 (including alternative salts, as well as pharmaceutically acceptable salts, including

alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives
2 of any one or more the aforementioned compounds.

In further aspects of the inventive subject matter, it should be appreciated that
4 contemplated compositions may further comprise additional active ingredients, including
compositions known to decrease a blood lipid concentration, and/or compositions known to
6 decrease blood sugar concentrations. For example, additional active ingredients may include
at least one of a vitamin and/or mineral preparation (including, but not limited to, chromium
8 and/or vanadium), metformin, sulfonylurea, thiazolidinediones (TZDs) and the like.

Preferred additional active ingredients include one or more of metformin, sulfonylurea,
10 pioglitazone and rosiglitazone.

In still further aspects of the invention, contemplated compositions increase glucose
12 uptake into a cell when present in a medium surrounding the cell, such as in the serum or
interstitial fluids. It is contemplated that the cell may be any cell including a myocyte or
14 other muscle cells, or part of a tissue. It is further contemplated that the cell may be insulin
dependent or insulin independent. Contemplated tissues are preferred to be *in vivo*, and may
16 include liver tissue, skeletal muscle tissue, pancreatic tissue, and adipose tissue. It is further
contemplated that the composition may increase glucose uptake into a cell when the
18 compound is present in a medium surrounding the cell at a concentration of between 0.1 to
100 micrograms per milliliter. In a preferred embodiment, the composition may increase
20 glucose uptake into a cell when the compound is present in a medium surrounding the cell at
a concentration of between 0.5 to 50 micrograms per milliliter. In another a preferred
22 embodiment, the composition may increase glucose uptake into a cell when the compound is
present in a medium surrounding the cell at a concentration of between 2 to 10 micrograms

per milliliter. In a preferred embodiment, 0.1 to 100 micrograms per milliliter. In a
2 preferred embodiment, the composition may increase glucose uptake into a cell when the
compound is present in a medium surrounding the cell at a concentration greater than one or
4 more of 0.1, 0.5, 1, 2, 5, 10, 25, 50 and 100 micrograms per milliliter. In a preferred
embodiment, the medium is blood. In a preferred embodiment, the medium is plasma.

6

E. Treatment Methods of the Invention

8 An advantageous aspect of the instant invention concerns the discovery that, when
administered in a therapeutically effective dose, compounds and compositions of the
10 invention, including pharmaceutical compositions, will reduce blood glucose concentrations
in an organism suffering from an elevated glucose concentration. While not wishing to be
12 bound by theory, applicants believe a mechanism involving the activation of AMPK and/or
Akt underlies the reduction in blood glucose that follows administration of a contemplated
14 compound, or a composition comprising a contemplated compound, including a
pharmaceutical composition, to an organism. As such, the utility of the inventive subject
16 matter additionally extends to methods for treating a variety of disorders that are ameliorated
through activation of AMPK and/or Akt, such as those disorders well known in the art
18 and/or exemplified in the instant application.

In a preferred aspect of the inventive subject matter, exposing an organism to a
20 contemplated compound, or a composition comprising a contemplated compound, including
a pharmaceutical composition, results in increased intracellular levels of activated AMPK
22 and/or activated Akt. In one embodiment, the organism is a tissue or cell isolated from a
whole organism. In another embodiment, the organism is a whole organism. In a preferred

embodiment, the organism is a whole human organism or a tissue or cell isolated therefrom.

2 In other preferred embodiments, the cell may be a myocyte or part of an *in vivo* tissue such
as liver tissue, skeletal muscle tissue, pancreatic tissue, or adipose tissue. An oocyte is one
4 example of a preferred organism that may be employed in a preferred process, where oocyte
activity increases in response to the increased intracellular levels of activated AMPK that
6 result from exposing the organism to the composition. In another preferred embodiment, the
cellular import, export or synthesis of a molecule is modulated in response to the increased
8 intracellular levels of activated AMPK and/or activated Akt that result from exposing the
organism to a contemplated compound, or a composition comprising a contemplated
10 compound. In a preferred embodiment, exposing the organism to a contemplated
compound, or a composition comprising a contemplated compound, increases cellular
12 glucose uptake. In a preferred embodiment, the compound increases glucose uptake in a
non-insulin dependent manner. In a further preferred embodiment, the increase in glucose
14 uptake is attenuated by the presence of L-N-mono-methyl-L-arginine at a concentration of
300 micromoles per liter.

16 In a preferred aspect of the inventive subject matter, a therapeutically effective dose
of a pharmaceutical composition, including a pharmaceutical and/or nutraceutical,
18 comprising a contemplated compound is orally administered to a human patient diagnosed
with non-insulin dependent diabetes mellitus (NIDDM) and having an elevated glucose
20 concentration. Among the beneficial results contemplated for the treatment is a reduction in
blood glucose concentrations in the patient. Thus, an exemplary method comprises treating
22 a person (e.g., diagnosed with NIDDM) having an increased blood concentration of glucose,
such as of approximately 150 mg/dl, for example. In a preferred embodiment, a

therapeutically effective dose of a pharmaceutical composition, including a pharmaceutical
2 and/or nutraceutical, comprising a contemplated compound is coadministered along with at
least one of a vitamin and/or mineral preparation (including, but not limited to, chromium
4 and/or vanadium), metformin, sulfonylurea, thiazolidinediones (TZDs) and the like. In a
preferred embodiment, a pharmaceutical composition, including a pharmaceutical and/or
6 nutraceutical, comprising a contemplated compound is coadministered along with at least
one of metformin, sulfonylurea, pioglitazone and rosiglitazone, or any other medication
8 useful in the treatment of diabetes.

With respect to the glucose concentration, it is generally contemplated that the
10 glucose concentration is a blood glucose concentration. However, further contemplated
glucose concentrations also include concentrations of glucose covalently or non-covalently
12 bound to molecules found within the organism, and especially contemplated alternative
glucose concentrations include concentrations of glycosylated proteins (*e.g.*, glycosylated
14 hemoglobin or collagen).

It should be especially appreciated that contemplated pharmaceutical compositions
16 not only reduce elevated blood glucose concentration in a human suffering from NIDDM,
but may also reduce blood glucose concentrations in individuals having elevated blood
18 glucose concentrations for reasons other than NIDDM, including obesity, dietary effects,
etc.

20 Since another advantage to the treatment with the contemplated compounds and
compositions, including pharmaceutical compositions, relates to blood concentration of total
22 cholesterol, treatment according to the inventive subject matter need not be limited to
patients having elevated blood glucose levels, but may also be indicated in many patients

having near normal blood concentrations of glucose. Thus, a exemplary method comprises
2 treating a person having an increased blood concentration of total cholesterol, such as above
280 mg/dl, for example.

4 It is especially contemplated that treatment according to the inventive subject matter
may also result in significant weight loss, particularly in persons with obesity, NIDDM, or
6 other condition associated with increased body weight. It is generally contemplated that the
treatment according to the inventive subject matter is not limited to reduction of blood
8 glucose alone, but may concomitantly, or alternatively, include reduction of a particular lipid
or lipid group. For example, slightly elevated total cholesterol (*e.g.*, 220 mg/dl) may be an
10 indication for treatment with the contemplated compounds and compositions. Alternatively,
it is contemplated that an imbalance between HDL and LDL (*i.e.* LDL>>HDL) may be
12 normalized employing a treatment according to the inventive subject matter. Similarly,
while the total cholesterol in the patient need not be elevated, treatment with the
14 contemplated method may still be indicated due to an elevated triglyceride level.

Furthermore, contemplated compounds and compositions may also advantageously
16 reduce elevated blood lipid concentrations, wherein blood lipids such as, for example,
triglycerides, fatty acids, HDL-cholesterol, and LDL-cholesterol. Moreover, contemplated
18 compositions and compounds include those that may reduce blood lipids concomitantly with
the reduction of blood glucose levels, or independent of the reduction of the blood glucose
20 level.

It should also be appreciated that treatment with contemplated compounds and
22 compositions containing them, including pharmaceutical compositions, is expected to
diminish, or reduce the rate of progression of, damage to the endothelium caused by

hyperglycemia and free fatty acids, and for this reason it should be useful in preventing and
2 treating various types of vascular disease associated with metabolic abnormalities, including
atherosclerotic vascular disease and, in particular, atherosclerosis associated with diabetes
4 and insulin resistance. (For example, see WO 01/10449 A1, the entirety of which is herein
incorporated by reference.) By virtue of its effects on glucose and fatty acid metabolism in
6 pericytes, this treatment should also be useful in treating and preventing the microvascular
complications of diabetes (such as chronic wounds, blindness, retinopathy and possibly
8 nephropathy). Furthermore, treatment with contemplated compounds and compositions
containing them, including pharmaceutical compositions, should also prove a useful tool as
10 a chronically administered therapeutic agent in a wide array of situations in which
endothelial cell integrity is compromised by stress, e.g., hyperglycemia, high plasma free
12 fatty acid levels and to the extent they are caused by alterations in glucose or fatty acid
metabolism possibly ischemia and inflammation.

14 Additional preferred embodiments include methods for activating adenosine 5'-
monophosphate-activated protein kinase (AMPK) in a patient in need thereof, the method
16 comprising administering to said patient a composition comprising a therapeutically
effective amount of a contemplated compound that activates AMPK, wherein the patient
18 suffers from a condition or disorder selected from the group consisting of: non-insulin
dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides,
20 hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL),
ischemia, hypoxia and glucocorticoid-induced apoptosis.

22 Preferred embodiments include methods for activating adenosine 5'-monophosphate-
activated protein kinase (AMPK) in a patient in need thereof, the method comprising

administering to said patient a composition comprising a therapeutically effective amount of
2 a contemplated compound that activates AMPK, wherein the method results in one or more
of the following: (1) reduces one or more of fatty acid synthesis, sterol synthesis,
4 triglyceride synthesis and fatty acid synthase gene expression; (2) ameliorates one or more
conditions or disorders that are characterized by elevations in one or more of the pathways
6 or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and
fatty acid synthase gene expression; (3) increases fatty acid oxidation and ketogenesis; (4)
8 inhibits lipogenesis and/or isoprenaline-stimulated lipolysis; (5) ameliorates one or more
conditions or disorders that are characterized by elevations in one or both of lipogenesis and
10 isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one
or both of these pathways; (6) decreases insulin secretion; (7) ameliorates one or more a
12 conditions or disorders that are characterized by elevated insulin secretion, or that are
exacerbated by insulin secretion; (8) enhances glucose uptake in muscle cells; (9)
14 ameliorates one or more conditions or disorders that are characterized by decreased glucose
uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in
16 muscle cells; (10) reduces levels of cytoplasmic HuR, which in turn, in reduces
concentrations and half-lives of target mRNA transcripts; (11) ameliorates one or more
18 conditions or disorders that are characterized decreased levels of HuR and its target
transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target
20 transcripts, which may, for example, play an important role in aging; (12) provides
protection against glucocorticoid-induced apoptosis; (13) ameliorates one or more
22 conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis,
or that are exacerbated by glucocorticoid-induced apoptosis; (14) protects against cellular

stresses resulting from ischemia; (15) inhibits adipogenesis; (16) ameliorates one or more
2 conditions or disorders that are characterized by increased adipogenesis, or that are
exacerbated by adipogenesis; (17) protects neurons against metabolic and excitotoxic insults
4 associated with the pathogenesis of a neurodegenerative condition; (18) promotes astrocytes
to produce ketone bodies as a substrate for neuronal oxidative metabolism; (19) increases
6 insulin sensitivity of muscle glucose transport; (20) protects against hepatic ischemia-
reperfusion (I/R) injury associated with liver transplantation and hepatic resections; (21)
8 lowers blood glucose concentrations by decreasing hepatic glucose production and/or
increasing glucose disposal in skeletal muscle; and (22) ameliorates one or more conditions
10 or disorders associated with insulin resistance syndrome through improving glucose
tolerance, improving lipid profile or reducing systolic blood pressure.

12 The duration for contemplated treatments may vary significantly, and suitable
durations may be within the range of a single dose, but also for a predetermined period,
14 including one week, several weeks, several months, and even several years. Consequently, it
should be appreciated that compositions according to the inventive subject matter may also
16 be prophylactically administered to a human to prevent hyperglycemia, or some form of
dyslipidemia.

18 Of course it should also be recognized that the form of administration may vary
considerably. For example, oral administration need not be limited to a tablet, and
20 alternative oral administrations may include powders, gel-caps, syrups, gels, etc. Where oral
administration is not desirable, it is further contemplated that alternative routes are also
22 appropriate, including injections, transdermal, pulmonary or intranasal delivery. (Various
formulations appropriate for use in the contemplated methods are discussed in detail in

Section D - "Pharmaceutical Compositions and Dietary Supplements of the Invention" of
2 the instant application.)

In further alternative aspects of the inventive subject matter, the composition may
4 also be administered to an organism other than a human, and particularly preferred
alternative organisms include livestock (*e.g.*, cattle, pigs, horses, etc.) and pets (*e.g.*, dogs,
6 cats, rodents, birds, etc.). With respect to contemplated compound and compositions, the
same considerations as described above apply.

8

Examples

10 Examples 1-17 exemplify various procedures, results and embodiments related to the
contemplated compounds, compositions and methods of the inventive subject matter.

12

Example 1

14 The levels of Glut-4, activated AMPK and activated Akt were measured in mouse
muscle cells C2C12 (from ATTC) and in primary culture of human skeletal muscle cells
16 (Clonetics, Inc.) using Western immunoblotting. C2C12 cells were plated at 1.5×10^5
cells per mL/well (12-well plate) in standard cell culture medium (DMEM supplemented
18 with 10% fetal bovine serum (FBS), 25mM glucose, 20mM Hepes, 4mM glutamine and 2
mM sodium pyruvate. 48 hrs after the plating, medium was changed to differentiation
20 medium (DMEM supplemented with 5 mM of glucose and 0.5% of FBS) for next 3-4 days
to stimulate the formation of myotubes. Three hrs before the treatment with selected agents,
22 cells were washed with PBS and transferred to PBS supplemented with 5mM of glucose.

Human skeletal muscle cells (HSKM) were cultured in SKBM-2 mediums provided by
2 Clonetics. 48 hrs after cell plating, medium was changed to SKBM medium to stimulate
differentiation of the cells to myotubes. When differentiated, the myotubes were transferred
4 to PBS supplemented with 5mM glucose for three hrs before the treatment.

Analysis of C2C12 cells for the level of activated AMPK, Akt and the level of
6 GLUT-4 was performed in the same experimental system. The cells were treated for 30
minutes at 37 °C. After the treatment, the cells were washed with ice-cold PBS and lysed
8 with 80ul of lysis buffer/well (M-PER buffer from Pierce supplemented with protease and
phosphatase inhibitor mix (Calbiochem) for 10 minutes on ice. Next, the plates were
10 transferred to -20 °C to improve the lysis of the cells. Next cells were sonicated for 5
minutes and lysate was transferred to Eppendorf tubes and centrifuged at 14,000rpm for 10
12 minutes. Supernatants were collected in fresh Eppendorf tubes and kept on ice to measure
the amount of total proteins. 3µl of each lysate was used to measure the protein
14 concentration using standard Bradford method (Biorad). Subsequently, 20µg per sample of
sample protein was used for Western analysis using NuPage 10% Bis/Tris gels (Invitrogen).
16 After exposure of membranes to primary and secondary antibodies AMPK, AKT or Glut-4
was detected using ECL-Plus (Amersham) following producer's instruction.
18 Chemilumiscent signals were detected by using ChemiDoc system from Biorad. Intensity of
detected signals were analyzed and measured using Quantity One software (Biorad).
20 Alternatively, the level of phosphorylated AMPK was detected using ECL kit from
Amersham and short exposure to Kodak films.

Experimental setup:

- 2 1. Cell Culture
2. Treatment
- 4 3. Cell Lysis
4. Western blot analysis
- 6 a. AMPK
- b. Akt
- 8 c. GLUT4
- d. Total AMPK
- 10 e. Total Akt
- 12 5. Signal measure

AMPK, AKT and GLUT-4 were measured from the same samples.

14 Primary antibodies used in these studies are the following:

1. Anti-phospho-AMPK (Thr172), mouse, rabbit IgG, from Cell Signaling, #2531
- 16 2. Anti-phospho-Akt (Ser473), mouse, rabbit IgG, Cell Signaling, #9271
3. Anti-Glut-4, mouse, rabbit IgG, Calbiochem, #400064
- 18 4. Anti-AMPK (total), mouse, rabbit IgG, Cell Signaling, #2532
5. Anti-Akt (total), mouse, rabbit IgG, Cell Signaling, #9272

20 The effects of various purine derivative, including cytokinins, on AMPK activity are
summarized in Table 5. The results demonstrate that most of the tested agents potently
22 stimulate AMPK activity, with some resulting in over 10 fold increases in activity compared
the untreated control. The more potent compounds includes derivatives of adenine, cytidine
24 and guanosine as well as kinetin and zeatin.

2

Table 5 – Effects on AMPK in C2C12 muscle cells *in vitro*

Agent	Concentration	Experiment No.	Fold AMPK Activation (over control)
Adenosine	μM 12.5	11-2	1.83
	5.0		1.64
	2.5		1.87
N6-Acetyl-Adenosine	μM 12.5	11-2	2.18
	5.0		2.41
	2.5		1.08
Benzyl-Adenine	μM 50.0	7-2	2.92
	5.0		2.70
	0.5		2.18
Gamma, Gamma-Dimethylallyl-6-Aminopurine	μM 50.0	7-2	2.11
	5.0		2.45
	0.5		2.82
Dihydro-Zeatin	μM 50.0	6-2	0.88
	5.0		0.59
	0.5		2.25
Zeatin	μM 1.0	112802	2.33
	10.0	112702	2.04
	1.0		2.15
Trans-Zeatin	μM 10.0	112702	4.27
	1.0		2.33
Guanosine	μM 5.0	19-2	3.70
N2-Acetyl-Guanosine	μM 2.0	19-2	2.20
	0.8		2.20
	0.3	23-1	3.75
	1.5		4.28
	7.5		1.71
	37.5		2.28
N2-Acetyl-Guanine	μM 0.3	23-1	5.42
	1.5		5.85
	7.5		6.00
	37.5		6.51
Kinetin	μM 0.8	19-2	3.60
	0.8	20-1	2.40
	2.0		2.70
	10.0		12.80
	0.1	17-4	5.30
	0.3		8.12
	1.0		19.50
	3.0		14.50
Kinetin Riboside	μM 3.0	17-4	12.00
Metformin	mM 2.0	23-3	1.42
Rosiglitazone	μM 3.0	19-2	3.50

The effects of various purine derivative, including cytokinins, on Akt activity are
2 summarized in Table 6. Many of the potent AMPK stimulators had only marginal effect on
Akt activity. For example, zeatin is a potent stimulator of AMPK but not Akt. However,
4 guanosine, N2-Acetyl-Guanosine and N2-Acetyl-Guanine were observed to be potent
activators of AMPK as well as Akt.

6

Table 6 – Effects on Akt in C2C12 muscle cells *in vitro*

Agent	Concentration	Experiment No.	Fold Akt Activation (over control)
Kinetin	μ M	14-6	5.0
			2.0
			0.8
		22-2	8.1
			2.7
			0.9
Kinetin Riboside	μ M	14-6	0.3
			5.0
			3.32
Zeatin	μ M	271102	2.0
			5.14
			3.71
Trans-Zeatin	μ M	271102	1.0
			10.0
			0.95
Gamma, Gamma-Dimethylallyl-6-Aminopurine	μ M	14-4	1.0
			2.0
			1.32
N4-Acetyl-Cytidine	μ M	14-6	0.8
			3.56
			5.0
		12-3	2.0
			1.64
			1.46
N2-Acetyl-Guanosine	μ M	11-10	0.8
			5.0
			1.36
		17-1	2.0
			1.50
			1.23
N2-Acetyl-Guanine	μ M	19-2	0.8
			2.17
			2.95
		23-1	7.5
			1.5
			0.3
AICAR	μ M	22-1	7.5
			1.5
			0.3
		23-1	7.5
			1.5
			0.3
Metformin	mM	22-1	500.0
			50.0
			20.0
Insulin	nM	14-3	2.0
			100.0
			50.0
Rosiglitazone	μ M	22-2	25.0
			0.71
			1.78
		17-6	3.0
			5.01
			2.83

The effects of kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine on GLUT-4 protein level in C2C12 cells were investigated following the same experimental design as described for AMPK and AKT. Anti-Glut-4 antibody used in this study was from Calbiochem. The results summarized in Table 7 demonstrate that kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine potently increase GLUT-4 protein level in C2C12 cells at different range and in a dose-dependent manner.

Table 7 – Effects on GLUT-4 in C2C12 muscle cells *in vitro*

Agent	Concentration		Experiment No.	Fold Change in GLUT-4 Level (over control)	
Rosiglitazone	μM	3.0	22-2	3.82	
		9.0		3.61	
		27.0		3.19	
		3.0	22-1	2.13	
		3.0	19-2	4.37	
Metformin Kinetin	mM	3.0	20-1	2.98	
		2.0	22-1	1.50	
	μM	0.3	22-2	3.45	
		0.9		4.00	
		2.7		3.88	
		8.1		1.11	
		0.8		19-2	3.46
		0.3		20-1	3.95
N2-Acetyl-Guanine	μM	0.8	22-2	2.36	
		2.0		1.88	
		0.3		3.94	
		1.5		3.84	
		7.5		3.24	
		37.5		2.80	
N2-Acetyl- Guanosine	μM	0.3	22-2	1.21	
		1.5		1.74	
		7.5		3.14	
		37.5		3.03	

Example 2

2 Total glucose uptake was measured using fluorescent glucose analog from Molecular
Probes. Briefly, muscle cells were treated with kinetin, N2-Acetyl-Guanosine and N2-
4 Acetyl-Guanine for 30 minutes at 37C first and subsequently, these cells were exposed to
500 μ M of fluorescent glucose analog for 5 minutes at room temperature. Next, cells were
6 washed twice with cold Krebs-Hepes buffered solution and fixed in 70% ethanol in water.
Fluorescence of fluorescent glucose in the cells was measured using fluorescent plate reader
8 at 480/530 nm (excitation/emission). The results summarized in Table 8 demonstrate that
kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine each potently enhance glucose
10 uptake in muscle cells *in vitro*.

Table 8 - Effects on Glucose Uptake in Muscle Cells *In Vitro*.

Agent	Concentration	Average Values (n=3)	Fold Change in Total Glucose Uptake (over control)
N2-Acetyl-Guanosine	μM	0.0	20.3 +/-0.1
		0.3	44.1 +/-0.7
		1.5	54.3 +/-0.9
		7.5	61.7 +/-1.3
		0.00	46.5 +/- 1.2
		0.15	90.5 +/- 1.7
		0.75	109.5 +/-2.6
		3.75	148.7 +/- 8.5
N2-Acetyl-Guanine	μM	0.3	54.5 +/- 1.7
		1.5	55.2 +/- 0.8
		7.5	59.6 +/-0.4
		0.00	46.5 +/-1.2
		0.15	86.4 +/- 2.3
		3.75	115.9 +/- 3.7
		0.00	47 +/- 0.7
		0.15	88.6 +/- 0.9
Kinetin	μM	0.75	103.3 +/-2.1
		3.75	102.6 +/-4.7
		0.0	28.9 +/-0.1
		0.3	86.0 +/-0.7
		1.5	110.6 +/-2.3
		7.5	56.6 +/-1.4
Rosiglitazone	μM	3.0	47.3 +/-1.1
		30.0	56.5 +/- 1.4
		0.0	52.1 +/-0.2
		3.0	122.4 +/-3.7

Example 3

2 The ability of a compound to increase the fermentation rate of yeast was evaluated as
a potential initial screen for selected compounds having a desired biological activity. The
4 fermentation rate of *Saccharomyces cerevisiae* was measured according to Warburg
methodology by determination of evolved carbon dioxide during fermentation process.

6 Dry commercial Baker's Yeast used in all experiments. The fermentation medium
comprised about 2.5% glucose in 63 mM phosphate buffer (pH 6.3). The effects of test
8 substances on the rate yeast fermentation were compared with the rate yeast fermentation in
control tests lacking the test substance.

10 Tests were conducted employing an apparatus comprising two parallel units for
simultaneous fermentation rate measurement in presence of the tested substance (Probe) and
12 in absence of it (Control). Units were identical consisting of the fermentation vessels
(Erlenmeyer flask, 100 ml) connected to a manometric U tube ($h \approx 25$ cm, diameter = 2 mm)
14 equipped with valve and filled with light liquid such as isopropanol. Erlenmeyer flasks were
equipped with magnetic stirring bars and placed on a magnetic stirrer (20-25 cm diameter).
16 Generally, the amount of yeast employed was fixed at about 50 mg, while the volume of
fermentation medium was generally about 20 mL. The amounts of tested substances varied
18 from 0.020 mg to 0.700 mg, depending on their activities.

 In a practical experiment both systems are simultaneously pre-incubated under
20 aerobic conditions for 10 minutes (open valves). Fermentation process under anaerobic
conditions and the real rate measurements start after closing the valves. The fermentation
22 rates were monitored 5 minute interval for 50 minutes by observing the differences of the
liquid heights in U-tubes (which differences correspond to a pressure difference between a

reaction vessel and an atmosphere - deltaP). The results summarized in Table 9 demonstrate that various of the contemplated compounds, including cis-zeatin, trans-zeatin, dihydro-zeatin, benzyl-adenine, gamma,gamma-dimethylallyl-6-aminopurine, kinetin riboside, N6-acetyl-adenosine, N2-acetyl-Guanosine, N4-acetyl-cytidine, enhance yeast fermentation rates.

Table 9 - Effects on Yeast Fermentation Rate

Tested substances	Concentration	Enhancement of Yeast Fermentation Rate (after 60 minutes; control=1)
Cis-Zeatin	6.2 μ M	1.44
Trans-Zeatin	8.9 μ M	1.17
Dihydro-Zeatin	9.1 μ M	1.738
Benzyl-Adenine	11.3 μ M	1.74
Gamma,gamma-dimethylallyl-6-aminopurine	21.3 μ M	1.92
Kinetin Riboside	101 μ M	1.67
N6-acetyl-Adenosine	30.7 μ M	1.92
N2-acetyl-Guanosine	13.3 μ M	1.98
N4-acetyl-Cytidine	15.1 μ M	2.05
AICAR	135.5 μ M (35 mg/L)	1.77

Example 4

Conditions and disorders associated with AMPK regulation of liver are among those treatable by administering a composition comprising a compound that activates AMPK. Acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) are two classical targets for the AMPK system, catalyzing the key regulatory steps in fatty

acid and sterol synthesis, respectively (Winder et al, Am J Physiol, 277: E1-10, 1999, the
entirety of which is herein incorporated by reference.) Activation of AMPK serves to inhibit
both these lipid biosynthetic pathways, as well as triglyceride synthesis. Moreover, it is
suggested that activated AMPK inhibits the L-type pyruvate kinase and fatty acid synthase
gene expression. Inactivation of ACC in the liver cell also leads to decreases in the
concentration of the product of ACC, i.e., malonyl-CoA, which has marked effects on fatty
acid oxidation. Malonyl-CoA is a potent inhibitor of carnitine palmitoyltransferase-1 (CPT-
1), the "gatekeeper" for entry of fatty acids into the mitochondria. In the liver, fatty acid
oxidation can be considered to be an essential component of the pathway for synthesis of
ketone bodies: increases in fatty acid oxidation lead to increased hepatic ketogenesis.
Administering the composition to activate AMPK in the liver would result in decreases in
fatty acid, triglyceride, and sterol synthesis and increases in fatty acid oxidation and
ketogenesis. Thus, treatment with the composition to increase AMPK activity is useful in
reducing fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase
gene expression, and in ameliorating disorders that are characterized by elevations in one or
more of these pathways or mechanisms, or that are exacerbated by the effects of one or more
of these pathways or mechanisms, as would be recognized by one of skill in the art.
Treatment with the composition to increase AMPK activity is also useful in increasing fatty
acid oxidation and ketogenesis where increased ketogenesis is desired as would be
recognized by one of skill in the art.

Example 6

Conditions and disorders associated with AMPK regulation of insulin secretion are among those treatable by administering a composition comprising a compound that activates AMPK. Activated AMPK is thought to inhibit insulin secretion. (*Ibid.*) Since the contemplated compounds activate AMPK, treatment with the composition is useful in decreasing insulin secretion and in ameliorating disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion, as would be recognized by one of skill in the art.

22 **Conditions and disorders associated with AMPK regulation of muscle metabolism**
 and glucose uptake are among those treatable by administering a composition comprising a

compound that activates AMPK. The effect of contraction on glucose uptake in muscle is
2 well documented. It has been observed that either of exercise or electrical stimulation of
muscle increases AMPK activity and also increases glucose uptake. It has also been
4 observed that glucose uptake is increased by chemical activation of AMPK with AICA-
riboside. Based on these observations, it has been hypothesized that muscle contraction
6 plays a role in stimulating glucose uptake in muscle, where one mechanism underlying
increased uptake stems from activated AMPK increasing GLUT-4 translocation from
8 microvesicles to sarcolemmal membranes in muscle. (*Ibid.*) Thus, treatment with the
composition to increase AMPK activity is useful in enhancing glucose uptake in muscle
10 cells, and in ameliorating disorders that are characterized by decreased glucose uptake in
muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle
12 cells, as would be recognized by one of skill in the art.

14 Example 8

Conditions and disorders associated with AMPK regulation of cytoplasmic
16 concentrations of HuR are among those treatable by administering a composition comprising
a compound that activates AMPK. HuR is an RNA binding protein that functions to
18 stabilize a variety of target mRNA transcripts, including those encoding p21, cyclinA and
cyclinB1. It has been shown that the presence of activated AMPK results in reduced levels
20 of cytoplasmic HuR, and in turn, in reduced concentrations and half-lives of mRNA
encoding p21, cyclinA and cyclinB1. (Mol Cell Biol, 22(10):345-36, 20002, the entirety of
22 which is herein incorporated by reference) Thus, treatment with the composition to increase
AMPK activity is useful in reducing levels of cytoplasmic HuR, and in turn, in reducing

concentrations and half-lives of a variety of target mRNA transcripts, including but not
2 limited to those encoding p21, cyclinA and cyclinB1, and in ameliorating disorders that are
characterized decreased levels of HuR and its target transcripts, or that are exacerbated by
4 the effects of decreased levels of HuR and its target transcripts, as would be recognized by
one of skill in the art.

6

Example 9

8 Conditions and disorders associated with AMPK regulation of glucocorticoid-
induced apoptosis are among those treatable by administering a composition comprising a
10 compound that activates AMPK. Activated AMPK has been shown to provide protection
against glucocorticoid-induced apoptosis and to restore cell viability and inhibit DNA
12 laddering in dexamethasone-treated thymocytes. (Biochem Biophys Res Commun,
243(3):821-6, 1998, the entirety of which is herein incorporated by reference) Furthermore,
14 activated AMPK has been shown to provide protection against dexamethasone-induced
activation of caspase 3-like enzymes, which are believed to play a pivotal role in apoptotic
16 cell death. Thus, treatment with the composition to increase AMPK activity is useful in
providing protection against glucocorticoid-induced apoptosis as would be recognized by
18 one of skill in the art, and in ameliorating disorders that are characterized by increased
glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced
20 apoptosis, as would be recognized by one of skill in the art.

22

Example 10

2 Conditions and disorders associated with AMPK regulation of cellular responses to
stresses, including ischemia, are among those treatable by administering a composition
4 comprising a compound that activates AMPK. In several non-vascular tissues in which it
has been studied, AMPK appears to modulate the cellular response to stresses such as
6 ischemia. In liver and muscle, AMPK phosphorylates and inhibits acetyl CoA carboxylase
(ACC), leading to an increase in fatty acid oxidation; and in muscle, its activation is
8 associated with an increase in glucose transport. Furthermore, incubation of human
umbilical vein endothelial cells (HUVEC) with an AMPK activator has been shown to cause
10 a 5-fold activation of AMPK, which was accompanied by a 70% decrease in ACC activity
and a 2-fold increase in fatty acid oxidation. (Biochem Biophys Res Commun, 265(1):112-5,
12 1999, the entirety of which is herein incorporated by reference) However, in this same
study, glucose uptake and glycolysis, the dominant energy-producing pathway in HUVEC,
14 were diminished by 40-60% under these conditions. Despite this, cellular ATP levels were
increased by 35%. Thus, treatment with the composition to increase AMPK activity is
16 expected to result in major alterations in endothelial cell energy balance, which are useful in
providing protection against cellular stresses in conditions including ischemia, as would be
18 recognized by one of skill in the art.

20 **Example 11**

 Conditions and disorders associated with adipogenesis are among those treatable by
22 administering a composition comprising a compound that activates AMPK. The AMPK
activator, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), has been found to

inhibit the differentiation of 3T3-L1 adipocytes, if added at an early phase of differentiation.
2 (Biochem Biophys Res Commun, 286(5):852-6, the entirety of which is herein incorporated
by reference). AICAR blocks the expression of the late adipogenic markers, fatty acid
4 synthase and acetyl-CoA carboxylase, and of the transcription factors, C/EBPalpha and
PPARgamma. It also inhibits early clonal expansion of pre-adipocytes, prevents the fall in
6 C/EBPbeta expression during the intermediate stage of differentiation and inhibits the late
phase expression of CHOP-10, an antagonist of C/EBPbeta. Thus, given the inhibitory role
8 for AMPK in the process of adipose differentiation, treatment with the composition to
increase AMPK activity is useful in inhibiting adipogenesis as would be recognized by one
10 of skill in the art, and in ameliorating conditions and disorders that are characterized by
increased adipogenesis, or that are exacerbated by adipogenesis, as would be recognized by
12 one of skill in the art.

14 **Example 12**

Conditions and disorders associated with metabolic and excitotoxic insults relevant
16 to the pathogenesis of several different neurodegenerative conditions are among those
treatable by administering a composition comprising a compound that activates AMPK. It is
18 well known that the brain has a high metabolic rate and is sensitive to changes in the supply
of glucose and oxygen. The expression of AMPK in embryonic and adult brain and its role
20 in modifying neuronal survival under conditions of cellular stress have been investigated. (J
Mol Neurosci, 17(1): 45-58, 2001, the entirety of which is herein incorporated by reference)
22 Catalytic (alpha1 and alpha2) and noncatalytic (beta2 and gamma1) subunits of AMPK are
present at high levels in embryonic hippocampal neurons in vivo and in cell culture. In the

adult brain, the catalytic subunits alpha1 and alpha2 are present in neurons throughout the
2 brain. The AMPK-activating agent AICAR protected hippocampal neurons against death
induced by glucose deprivation, chemical hypoxia, and exposure to glutamate and amyloid
4 beta-peptide. Suppression of levels of the AMPK alpha1 and alpha2 subunits using antisense
technology resulted in enhanced neuronal death following glucose deprivation, and
6 abolished the neuroprotective effect of AICAR. Thus, given the role of AMPK activation in
modifying neuronal survival under conditions of cellular stress, treatment with the
8 composition to increase AMPK activity is useful in protecting neurons against metabolic
and excitotoxic insults relevant to the pathogenesis of several different neurodegenerative
10 conditions as would be recognized by one of skill in the art.

12 **Example 13**

Conditions and disorders associated with hypoxia are among those treatable by
14 administering a composition comprising a compound that activates AMPK. AMPK is
believed to play a role in regulating ketone body production by astrocytes. (J Neurochem,
16 73(4): 1674-82, 1999, the entirety of which is herein incorporated by reference). Incubation
of astrocytes with AICAR has been shown to stimulate both ketogenesis from palmitate and
18 carnitine palmitoyltransferase I concomitant to a decrease of intracellular malonyl-CoA
levels and an inhibition of acetyl-CoA carboxylase/fatty acid synthesis and 3-hydroxy-3-
20 methylglutaryl-CoA reductase/cholesterol synthesis. Moreover, microdialysis experiments
have shown AICAR to stimulate brain ketogenesis markedly. Incubation of astrocytes with
22 azide has been shown to lead to a remarkable drop of fatty acid beta-oxidation. However,
activation of AMPK during hypoxia was shown to compensate the depression of beta-

oxidation, thereby sustaining ketone body production. The effect is believed to rely on the
2 following cascade: hypoxia => increase of the AMP/ATP ratio => AMPK stimulation =>
acetyl-CoA carboxylase inhibition => decrease of malonyl-CoA concentration => carnitine
4 palmitoyltransferase I deinhibition => enhanced ketogenesis. Furthermore, incubation of
neurons with azide has been shown to blunt lactate oxidation, but not 3-hydroxybutyrate
6 oxidation. Thus, given the role of AMPK activation in regulating ketone body production by
astrocytes, treatment with the composition to increase AMPK activity is useful in promoting
8 astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism during
hypoxia.

10

Example 14

12 Conditions and disorders associated with diminished insulin sensitivity of muscle
glucose transport are treatable by administering a composition comprising a compound that
14 activates AMPK. A study to determine the degree to which hypoxia and AICAR, which
also activate AMPK and stimulate glucose transport, also induce an increase in insulin
16 sensitivity has been reported. (Am J Physiol Endocrinol Metab, 282(1): E18-23, 2002, the
entirety of which is herein incorporated by reference) The study found that the increase in
18 glucose transport in response to 30 microU/ml insulin was about two-fold greater in rat
epitrochlearis muscles that had been made hypoxic or treated with AICAR 3.5 h previously
20 than in untreated control muscles. This increase in insulin sensitivity was similar to that
induced by a 2-h bout of swimming or 10 min of in vitro electrically stimulated contractions.
22 Neither phosphatidylinositol 3-kinase activity nor protein kinase B (PKB) phosphorylation
in response to 30 microU/ml insulin was enhanced by prior exercise or AICAR treatment

that increased insulin sensitivity of glucose transport. Inhibition of protein synthesis by
2 inclusion of cycloheximide in the incubation medium for 3.5 h after exercise did not prevent
the increase in insulin sensitivity. Contractions, hypoxia, and treatment with AICAR all
4 caused a two- to three-fold increase in AMPK activity over the resting level. These results
provide evidence that the increase in insulin sensitivity of muscle glucose transport that
6 follows exercise is mediated by activation of AMPK. Thus, treatment with the composition
to increase AMPK activity is useful in increasing insulin sensitivity of muscle glucose
8 transport.

10 **Example 15**

Occurrences of hepatic ischemia-reperfusion (I/R) injury associated with liver
12 transplantation and hepatic resections can be reduced by administering a composition
comprising a compound that activates AMPK. Preconditioning is known to preserve energy
14 metabolism in liver during sustained ischemia. A study has been reported that investigates:
1) whether preconditioning induces AMPK activation; and 2) if AMPK activation leads to
16 ATP preservation and reduced lactate accumulation during prolonged ischemia and its
relationship with NO. (Hepatology, 34(6): 1164-73, 2001, the entirety of which is herein
18 incorporated by reference) Preconditioning was reported to activate AMPK and
concomitantly reduce ATP degradation, lactate accumulation, and hepatic injury. The
20 administration of an AMPK activator, AICAR, before ischemia simulated the benefits of
preconditioning on energy metabolism and hepatic injury. The inhibition of AMPK
22 abolished the protective effects of preconditioning. The effect of AMPK on energy
metabolism was independent of NO because the inhibition of NO synthesis in the

preconditioned group and the administration of the NO donor before ischemia, or to the
2 preconditioned group with previous inhibition of AMPK, had no effect on energy
metabolism. Thus, given the role of AMPK activation in the protective effect against
4 ischemia, treatment with the composition to increase AMPK activity is useful in surgical
and pharmacological strategies aimed at reducing hepatic I/R injury.

6

Example 16

8 Conditions and disorders associated with hyperglycemia are treatable by
administering a composition comprising a compound that activates AMPK. It has recently
10 been reported that therapeutic doses of metformin increase AMPK activity in vivo in
subjects with type 2 diabetes. (Diabetes, 51(7): 2074-81, 2002, the entirety of which is
12 herein incorporated by reference) Metformin treatment for 10 weeks significantly increased
AMPK alpha2 activity in the skeletal muscle, and this was associated with increased
14 phosphorylation of AMPK on Thr172 and decreased acetyl-CoA carboxylase-2 activity. The
increase in AMPK alpha2 activity was likely due to a change in muscle energy status
16 because ATP and phosphocreatine concentrations were lower after metformin treatment.
Metformin-induced increases in AMPK activity were associated with higher rates of glucose
18 disposal and muscle glycogen concentrations. These findings suggest that the metabolic
effects of metformin in subjects with type 2 diabetes may be mediated by the activation of
20 AMPK alpha2. Given the hypoglycemic effect imparted by the activation of AMPK,
treatment with the composition to increase AMPK activity is useful to lower blood glucose
22 concentrations by decreasing hepatic glucose production and increasing glucose disposal in
skeletal muscle.

2

Example 17

Conditions and disorders associated with insulin resistance syndrome are treatable by
administering a composition comprising a compound that activates AMPK. Insulin
resistance syndrome is associated with obesity, type 2 diabetes, and muscle paralysis. (WO
01/97816 A1 and WO 01/93874 A1, the entireties of which are herein incorporated by
reference.) Insulin resistance syndrome is also associated with several risk factors for
cardiovascular disease. Chronic chemical activation of AMP-activated protein kinase by the
adenosine analog AICAR has been shown to augment insulin action, upregulate
mitochondrial enzymes in skeletal muscles, and decrease the content of intra-abdominal fat,
including that occurring in obesity. (WO 01/93873 A1, the entirety of which is herein
incorporated by reference.) Furthermore, acute AICAR exposure has been found to reduce
sterol and fatty acid synthesis in rat hepatocytes incubated in vitro as well as suppress
endogenous glucose production in rats under euglycemic clamp conditions. A recent study
investigated whether chronic AICAR administration, in addition to the beneficial effects on
insulin sensitivity in type 2 diabetes, is capable of improving other phenotypes associated
with the insulin resistance syndrome. (Diabetes, 51(7): 2199-206, 2002, the entirety of
which is herein incorporated by reference) AICAR administration significantly reduced
plasma triglyceride levels ($P < 0.01$ for AICAR vs. AL, and $P = 0.05$ for AICAR vs. PF) and
free fatty acids ($P < 0.01$ for AICAR vs. AL, and $P < 0.05$ for AICAR vs. PF) and increased
HDL cholesterol levels ($P < 0.01$ for AICAR vs. AL and PF). AICAR treatment also
lowered systolic blood pressure by 14.6 ± 4.3 mmHg ($P < 0.05$), and AICAR-treated
animals exhibited a tendency toward decreased intra-abdominal fat content. Furthermore,

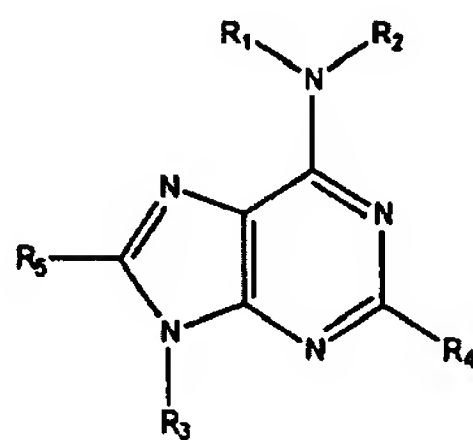
AICAR administration normalized the oral glucose tolerance test and decreased fasting
2 concentrations of glucose and insulin close to the level of the lean animals. Finally, in line
with previous findings, AICAR treatment was also found to enhance GLUT4 protein
4 expression and to increase maximally insulin-stimulated glucose transport in primarily white
fast-twitch muscles. In view of the strong evidence that activating AMPK improves glucose
6 tolerance, improves the lipid profile, and reduces systolic blood pressure, treatment with the
composition to increase AMPK activity is useful to reduce metabolic disturbances and
8 lowers blood pressure characteristic of insulin resistance syndrome.

While a number of embodiments of this invention have been herein before described,
10 it is apparent that the basic embodiments can be altered to provide other embodiments of the
disclosed invention. Therefore, it will be appreciated that the scope of this invention
12 includes all alternative embodiments and variations which are described in the foregoing
specification and by the claims appended hereto. The invention is not to be limited by the
14 specific embodiments that have been presented herein by way of example.

CLAIMS

We claim:

1. A pharmaceutical composition comprising a unit dosage of a cytokinin having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl, alkenyl or alkynyl.

2. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
3. The pharmaceutical composition of claim 2, wherein the cytokinin is selected from one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a hydrate, solvate, tautomer, and/or pharmaceutically acceptable salt thereof.
4. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: a naturally occurring cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
5. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: a non-naturally occurring cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-

zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 6, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminopurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
8. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
9. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: dihydro-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

10. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: cis-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
11. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: trans-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
12. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
13. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
14. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-benzyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-benzyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
16. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: kinetin (6-furfurylaminopurine), and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
17. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: kinetin riboside, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
18. A pharmaceutical composition comprising a unit dosage of one or more of: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-

isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of claim 18, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminopurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
21. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: dihydro-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
22. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: cis-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
23. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: trans-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
24. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

25. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
26. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-benzyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
27. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-benzyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
28. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: kinetin (6-furfurylaminopurine), and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
29. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: kinetin riboside, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

30. The pharmaceutical composition of any one of claims 1-29, wherein the unit dosage comprises a cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.
31. The pharmaceutical composition of claim 30, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 20% over pre-administration levels.
32. The pharmaceutical composition of claim 31, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 30% over pre-administration levels.
33. The pharmaceutical composition of claim 32, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of

activated Akt in one or more cell types and/or tissue types of said patient by at least 50% over pre-administration levels.

34. The pharmaceutical composition of claim 33, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 75% over pre-administration levels.
35. The pharmaceutical composition of claim 34, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold over pre-administration levels.
36. The pharmaceutical composition of claim 35, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold over pre-administration levels.
37. The pharmaceutical composition of claim 36, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold over pre-administration levels.

38. The pharmaceutical composition of any one of claims 30-37, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
39. The pharmaceutical composition of any one of claims 30-37, wherein the one or more cell types and/or tissue types include myocytes.
40. The pharmaceutical composition of any one of claims 1-39 wherein the pharmaceutical composition is in a form suitable for oral ingestion.
41. The pharmaceutical composition of claim 40, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.
42. The pharmaceutical composition of any one of claims 1-39, wherein the pharmaceutical composition is in a form suitable for parenteral injection.
43. The pharmaceutical composition of any one of claims 1-42, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

44. The pharmaceutical composition of any one of claims 1-43, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.
45. The pharmaceutical composition of claim 44, wherein the additional therapeutic ingredient is an anti-diabetic agent.
46. The pharmaceutical composition of claim 45, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.
47. The pharmaceutical composition of claim 46, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
48. The pharmaceutical composition of any one of claims 1-47, wherein the one or more cytokinins comprise, in total, at least 1%, by weight, of the pharmaceutical composition.
49. The pharmaceutical composition of claim 48, wherein one or more cytokinins comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

50. The pharmaceutical composition of any one of claims 1-49, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.
51. The pharmaceutical composition of any one of claims 1-50, wherein the pharmaceutical composition consists essentially of a cytokinin and a pharmaceutical carrier.
52. The pharmaceutical composition of any one of claims 1-51, comprising one or more cytokinins purified from a plant or yeast extract.
53. The pharmaceutical composition of any one of claims 1-51, consisting essentially of:
- (a) one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminopurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
 - (b) a pharmaceutically acceptable carrier; and optionally
 - (c) one or more additional agents to treat diabetes.
54. The pharmaceutical composition of any one of claims 1-51, consisting essentially of:
- (a) one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-

adenosine, kinetin (6-furfurylaminopurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

55. A method for treating or preventing diabetes comprising administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 1-54.
56. A method of decreasing blood glucose level comprising administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.
57. A method of treating impaired glucose tolerance comprising administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.
58. The method according to any of claims 55, 56 and 57, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

59. The method according to claim 58 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.
60. A method of treating or preventing diabetes comprising administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 1-54 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.
61. The method of claim 60, wherein the agent or agents to treat diabetes include one or more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.
62. The method of claim 61, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
63. The method of claim 60, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.
64. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising: providing a patient suffering from or believed to be at risk of

suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.

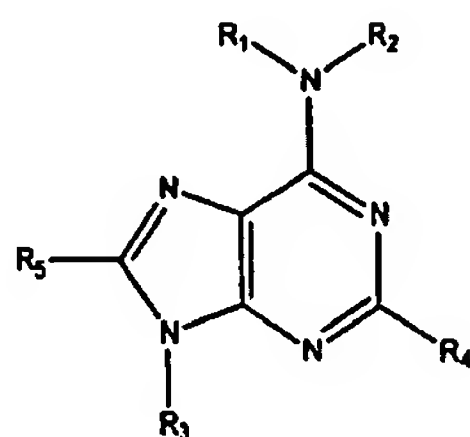
65. The method of claim 64, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.
66. The method of claim 65, wherein said disease or condition is atherosclerotic vascular disease.
67. The method of claim 64, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.
68. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.
69. The method of claim 68, wherein the patient suffers from obesity.

70. The method of claim 68, wherein the patient suffers from insulin resistance.
71. The method of claim 68, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.
72. The method of claim 68, wherein the method results in one or more of the following:
- (1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
 - (2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
 - (3) increases fatty acid oxidation and ketogenesis;
 - (4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;
 - (5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;
 - (6) decreases insulin secretion;
 - (7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;
 - (8) enhances glucose uptake in muscle cells;

- (9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;
- (10) reduces levels of cytoplasmic HuR, which in turn, reduces concentrations and half-lives of target mRNA transcripts;
- (11) ameliorates one or more conditions or disorders that are characterized by decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;
- (12) provides protection against glucocorticoid-induced apoptosis;
- (13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;
- (14) protects against cellular stresses resulting from ischemia;
- (15) inhibits adipogenesis;
- (16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;
- (17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;
- (18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;
- (19) increases insulin sensitivity of muscle glucose transport;
- (20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;
- (21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and
- (22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

73. The method of any one of claims 55-72, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

74. A pharmaceutical composition comprising a unit dosage of an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

75. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: an acyl-adenosine and an acyl-adenine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
76. The pharmaceutical composition of claim 75, wherein the adenine derivative is selected from one or more of: a mono-acyl-adenosine and a mono-acyl-adenine; and/or a hydrate, solvate, tautomer, and/or pharmaceutically acceptable salt thereof.
77. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: an N6-acyl-adenine and an N6-acyl-adenosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
78. The pharmaceutical composition of claim 77, wherein the adenine derivative is selected from one or more of: N6-acetyl-adenine and N6-acetyl-adenosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

79. The pharmaceutical composition of claim 78, wherein the adenine derivative is selected from one or more of: a naturally occurring N6-acetyl-adenine and a naturally occurring N6-acetyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
80. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: a non-naturally occurring adenine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
81. The pharmaceutical composition of any one of claims 74-80, wherein the unit dosage comprises adenine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.
82. The pharmaceutical composition of claim 81, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of

activated Akt in one or more cell types and/or tissue types of said patient by at least 20% over pre-administration levels.

83. The pharmaceutical composition of claim 82, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 30% over pre-administration levels.
84. The pharmaceutical composition of claim 83, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 50% over pre-administration levels.
85. The pharmaceutical composition of claim 84, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 75% over pre-administration levels.
86. The pharmaceutical composition of claim 85, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold over pre-administration levels.

87. The pharmaceutical composition of claim 86, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold over pre-administration levels.
88. The pharmaceutical composition of claim 87, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold over pre-administration levels.
89. The pharmaceutical composition of any one of claims 81-88, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
90. The method of any one of claims 81-88, wherein the one or more cell types and/or tissue types include myocytes.
91. The pharmaceutical composition of any one of claims 74-90 wherein the pharmaceutical composition is in a form suitable for oral ingestion.

92. The pharmaceutical composition of claim 91, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.
93. The pharmaceutical composition of any one of claims 74-90, wherein the pharmaceutical composition is in a form suitable parenteral injection.
94. The pharmaceutical composition of any one of claims 74-93, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.
95. The pharmaceutical composition of any one of claims 74-94, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.
96. The pharmaceutical composition of claim 95, wherein the additional therapeutic ingredient is an anti-diabetic agent.
97. The pharmaceutical composition of claim 96, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.
98. The pharmaceutical composition of claim 97, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

99. The pharmaceutical composition of any one of claims 74-98, wherein one or more adenine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.
100. The pharmaceutical composition of claim 99, wherein one or more adenine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.
101. The pharmaceutical composition of any one of claims 74-100, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.
102. The pharmaceutical composition of any one of claims 74-101, wherein the pharmaceutical composition consists essentially of an adenine derivative and a pharmaceutical carrier.
103. The pharmaceutical composition of any one of claims 74-102, comprising one or more adenine derivatives purified from a plant or yeast extract.

104. The pharmaceutical composition of any one of claims 74-103, consisting essentially of:
- (a) one or more of: an adenine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
 - (b) a pharmaceutically acceptable carrier; and optionally
 - (c) one or more additional agents to treat diabetes.
105. The pharmaceutical composition of any one of claims 74-104, consisting essentially of:
- (a) one or more of: an adenine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
 - (b) a pharmaceutically acceptable carrier.
106. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 74-105.

107. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.
108. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.
109. The method according to any of claims 106, 107 and 108, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.
110. The method according to claim 109 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.
111. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 74-105 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.

112. The method of claim 111, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.
113. The method of claim 112, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
114. The method of claim 111, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.
115. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.
116. The method of claim 115, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.

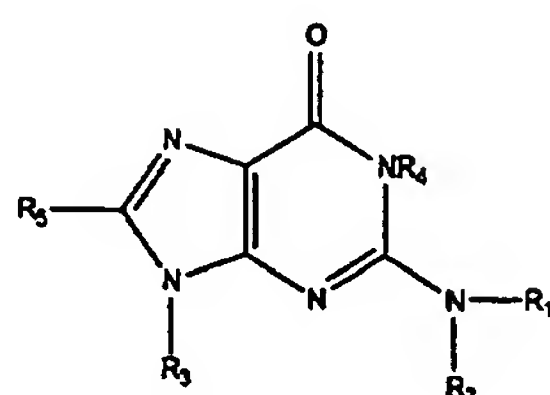
117. The method of claim 116, wherein said disease or condition is atherosclerotic vascular disease.
118. The method of claim 115, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.
119. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.
120. The method of claim 119, wherein the patient suffers from obesity.
121. The method of claim 119, wherein the patient suffers from insulin resistance.
122. The method of claim 119, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

123. The method of claim 119, wherein the method results in one or more of the following:

- (1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
- (2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
- (3) increases fatty acid oxidation and ketogenesis;
- (4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;
- (5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;
- (6) decreases insulin secretion;
- (7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;
- (8) enhances glucose uptake in muscle cells;
- (9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;
- (10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;
- (11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;
- (12) provides protection against glucocorticoid-induced apoptosis;
- (13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;

- (14) protects against cellular stresses resulting from ischemia;
 - (15) inhibits adipogenesis;
 - (16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;
 - (17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;
 - (18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;
 - (19) increases insulin sensitivity of muscle glucose transport;
 - (20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;
 - (21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and
 - (22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.
124. The method of any one of claims 106-123, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

125. A pharmaceutical composition comprising a unit dosage of a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

126. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: an acyl-guanosine and an acyl-guanine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
127. The pharmaceutical composition of claim 126, wherein the unit dosage comprises one or more of: a mono-acyl-guanosine and a mono-acyl-guanine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
128. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: an N6-acyl-guanine and an N6-acyl-guanosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
129. The pharmaceutical composition of claim 128, wherein the unit dosage comprises one or more of: N6-acetyl-guanine and N6-acetyl-guanosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
130. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: a naturally occurring guanine derivative, and/or a racemate,

enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or
pharmaceutically acceptable salt thereof.

131. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: a non-naturally occurring guanine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
132. The pharmaceutical composition of any one of claims 125-131, wherein the unit dosage comprises guanine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.
133. The pharmaceutical composition of claim 132, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold.

134. The pharmaceutical composition of claim 133, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold.
135. The pharmaceutical composition of claim 134, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold.
136. The pharmaceutical composition of any one of claims 132-135, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
137. The method of any one of claims 132-135, wherein the one or more cell types and/or tissue types include myocytes.
138. The pharmaceutical composition of any one of claims 125-137, wherein the pharmaceutical composition is in a form suitable for oral ingestion.

139. The pharmaceutical composition of claim 138, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.
140. The pharmaceutical composition of any one of claims 125-137, wherein the pharmaceutical composition is in a form suitable parenteral injection.
141. The pharmaceutical composition of any one of claims 125-140, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.
142. The pharmaceutical composition of any one of claims 125-141, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.
143. The pharmaceutical composition of claim 142, wherein the additional therapeutic ingredient is an anti-diabetic agent.
144. The pharmaceutical composition of claim 143, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.
145. The pharmaceutical composition of claim 144, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

146. The pharmaceutical composition of any one of claims 125-145, wherein one or more guanine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.
147. The pharmaceutical composition of claim 146, wherein one or more guanine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.
148. The pharmaceutical composition of any one of claims 125-147, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.
149. The pharmaceutical composition of any one of claims 125-148, wherein the pharmaceutical composition consists essentially of a guanine derivative and a pharmaceutical carrier.
150. The pharmaceutical composition of any one of claims 125-149, comprising one or more guanine derivatives purified from a plant or yeast extract.

151. The pharmaceutical composition of any one of claims 125-150, consisting essentially of:

- (a) one or more of: a guanine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
- (b) a pharmaceutically acceptable carrier; and optionally
- (c) one or more additional agents to treat diabetes.

152. The pharmaceutical composition of any one of claims 125-151, consisting essentially of:

- (a) one or more of: a guanine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
- (b) a pharmaceutically acceptable carrier.

153. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 125-152.

154. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.

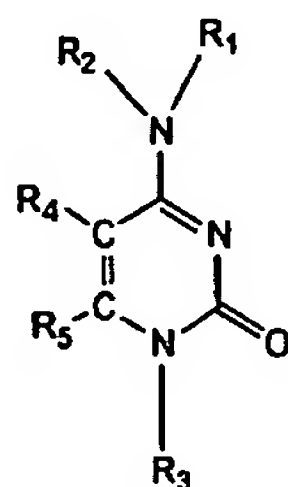
155. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.
156. The method according to any of claims 153, 154 and 155, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.
157. The method according to claim 156 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.
158. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 125-152 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.
159. The method of claim 158, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.

160. The method of claim 159, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
161. The method of claim 158, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.
162. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.
163. The method of claim 162, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.
164. The method of claim 163, wherein said disease or condition is atherosclerotic vascular disease.

165. The method of claim 162, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.
166. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.
167. The method of claim 166, wherein the patient suffers from obesity.
168. The method of claim 166, wherein the patient suffers from insulin resistance.
169. The method of claim 166, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.
170. The method of claim 166, wherein the method results in one or more of the following:
- (1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

- (2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
- (3) increases fatty acid oxidation and ketogenesis;
- (4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;
- (5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;
- (6) decreases insulin secretion;
- (7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;
- (8) enhances glucose uptake in muscle cells;
- (9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;
- (10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;
- (11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;
- (12) provides protection against glucocorticoid-induced apoptosis;
- (13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;
- (14) protects against cellular stresses resulting from ischemia;
- (15) inhibits adipogenesis;

- (16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;
 - (17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;
 - (18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;
 - (19) increases insulin sensitivity of muscle glucose transport;
 - (20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;
 - (21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and
 - (22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.
171. The method of any one of claims 153-170, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.
172. A pharmaceutical composition comprising a unit dosage of a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

173. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: an acyl-cytidine and an acyl-cytosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

174. The pharmaceutical composition of claim 173, wherein the unit dosage comprises one or more of: a mono-acyl-cytidine and a mono-acyl-cytosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

175. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: an N6-acyl-cytosine and an N6-acyl-cytidine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
176. The pharmaceutical composition of claim 175, wherein the unit dosage comprises one or more of: N6-acetyl-cytosine and N6-acetyl-cytidine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
177. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: a naturally occurring cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.
178. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: a non-naturally occurring cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

179. The pharmaceutical composition of any one of claims 172-178, wherein the unit dosage comprises a cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.
180. The pharmaceutical composition of claim 179, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold.
181. The pharmaceutical composition of claim 180, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold.
182. The pharmaceutical composition of claim 181, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold.

183. The pharmaceutical composition of any one of claims 179-182, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
184. The method of any one of claims 179-183, wherein the one or more cell types and/or tissue types include myocytes.
185. The pharmaceutical composition of any one of claims 172-184, wherein the pharmaceutical composition is in a form suitable for oral ingestion.
186. The pharmaceutical composition of claim 185, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.
187. The pharmaceutical composition of any one of claims 172-184, wherein the pharmaceutical composition is in a form suitable parenteral injection.
188. The pharmaceutical composition of any one of claims 172-187, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

189. The pharmaceutical composition of any one of claims 172-188, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.
190. The pharmaceutical composition of claim 189, wherein the additional therapeutic ingredient is an anti-diabetic agent.
191. The pharmaceutical composition of claim 190, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.
192. The pharmaceutical composition of claim 191, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
193. The pharmaceutical composition of any one of claims 172-192, wherein one or more cytosine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.
194. The pharmaceutical composition of claim 193, wherein one or more cytosine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

195. The pharmaceutical composition of any one of claims 172-194, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.
196. The pharmaceutical composition of any one of claims 172-195, wherein the pharmaceutical composition consists essentially of a cytosine derivative and a pharmaceutical carrier.
197. The pharmaceutical composition of any one of claims 172-196, comprising one or more cytosine derivatives purified from a plant or yeast extract.
198. The pharmaceutical composition of any one of claims 172-197, consisting essentially of:
- (a) one or more of: a cytosine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
 - (b) a pharmaceutically acceptable carrier; and optionally
 - (c) one or more additional agents to treat diabetes.

199. The pharmaceutical composition of any one of claims 172-198, consisting essentially of:
- (a) one or more of: a cytosine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and
 - (b) a pharmaceutically acceptable carrier.
200. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 172-199.
201. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 172-199.
202. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.
203. The method according to any of claims 200, 201 and 202, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

204. The method according to claim 203, wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.
205. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 272-199 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.
206. The method of claim 205, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.
207. The method of claim 206, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.
208. The method of claim 205, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.
209. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said

method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.

- 210. The method of claim 209, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.
- 211. The method of claim 210, wherein said disease or condition is atherosclerotic vascular disease.
- 212. The method of claim 209, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.
- 213. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.
- 214. The method of claim 213, wherein the patient suffers from obesity.

215. The method of claim 213, wherein the patient suffers from insulin resistance.
216. The method of claim 213, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.
217. The method of claim 213, wherein the method results in one or more of the following:
- (1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
 - (2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;
 - (3) increases fatty acid oxidation and ketogenesis;
 - (4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;
 - (5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;
 - (6) decreases insulin secretion;
 - (7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;

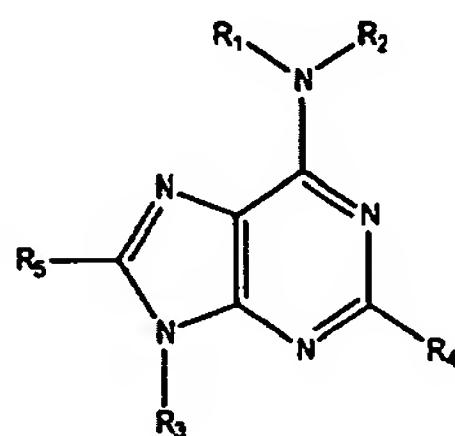
- (8) enhances glucose uptake in muscle cells;
- (9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;
- (10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;
- (11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;
- (12) provides protection against glucocorticoid-induced apoptosis;
- (13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;
- (14) protects against cellular stresses resulting from ischemia;
- (15) inhibits adipogenesis;
- (16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;
- (17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;
- (18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;
- (19) increases insulin sensitivity of muscle glucose transport;
- (20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;
- (21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and
- (22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

218. The method of any one of claims 200-217, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

219. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

- 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a cytokinin having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

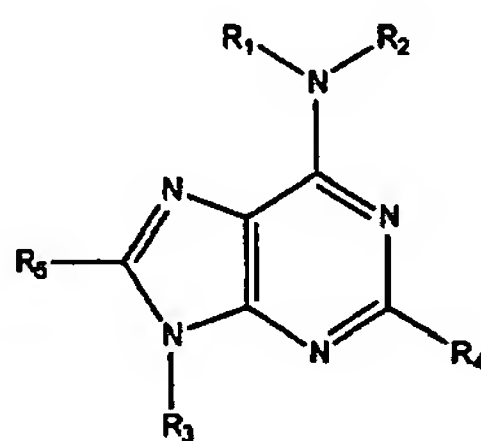
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and

- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

220. The method of claim 219, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,
wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

221. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

- 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is one or more cytokinins selected from:

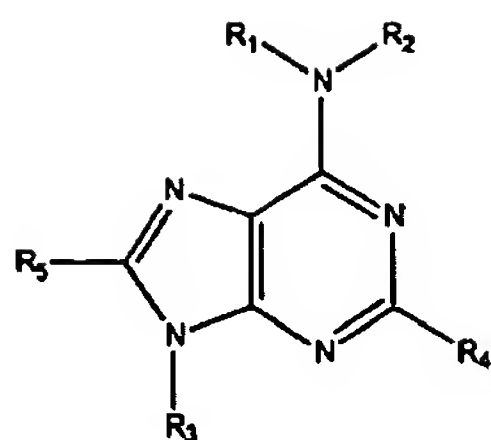
N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium

salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

222. The method of claim 221, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate

sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

223. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:
- 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and
 - 2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;
- wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

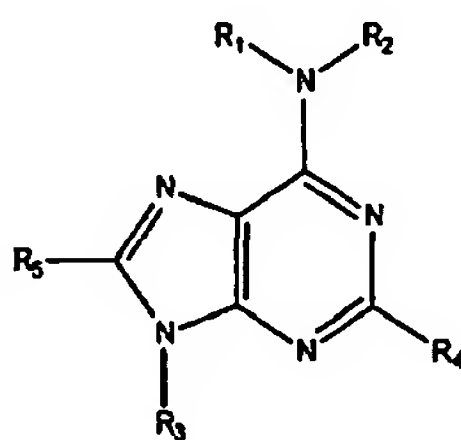
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

224. The method of claim 223, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

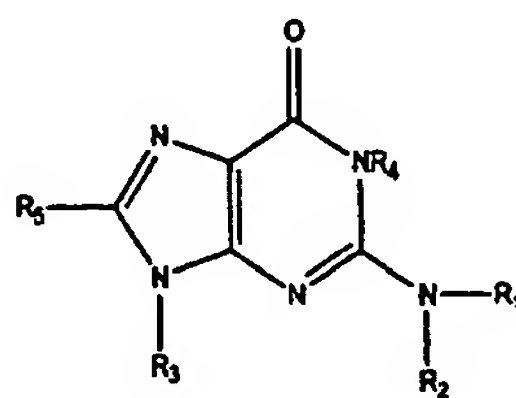
wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

225. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

- 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

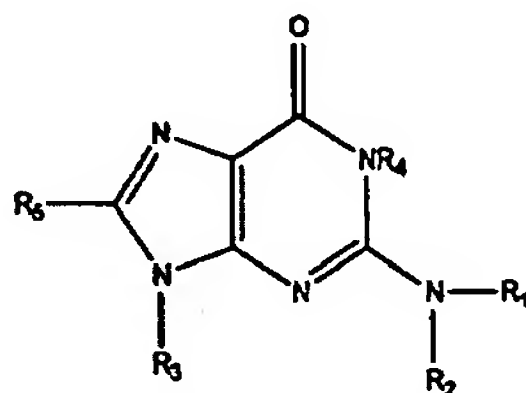
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

226. The method of claim 225, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, wherein:

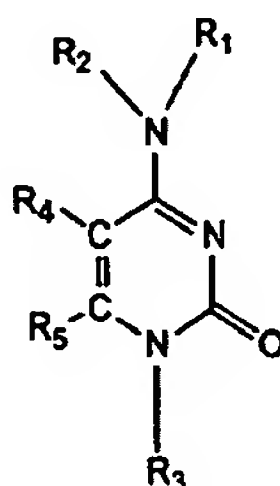
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

227. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:
- 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and
 - 2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

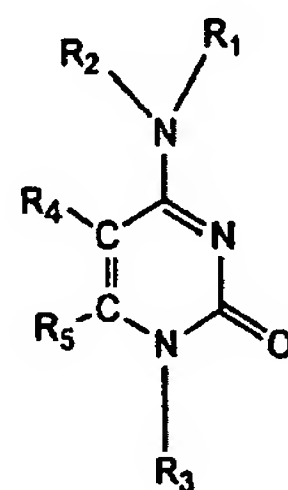
- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

228. The method of claim 227, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

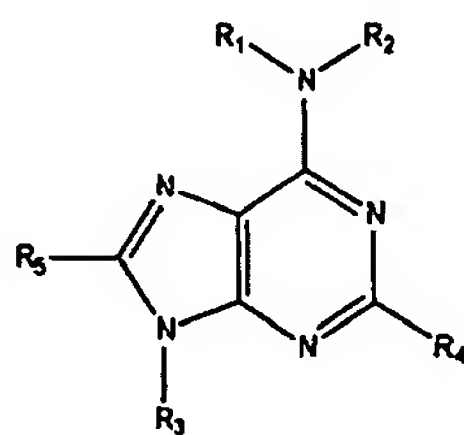
wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

229. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises (i) measuring the phosphorylation of AMPK and/or (ii) measuring the phosphorylation of a protein that is phosphorylated by AMPK.
230. The method of claim 229, wherein measuring the indicator of cellular AMPK activity comprises measuring the phosphorylation of AMPK.
231. The method of claim 230, wherein measuring the phosphorylation of AMPK comprises measuring the phosphorylation of the threonine 172 residue of AMPK.
232. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises measuring the phosphorylation of a protein that is phosphorylated by AMPK.

233. The method of claim 232, wherein the protein that is phosphoralated by AMPK is one of more proteins selected from the AMARA peptide and the SAMS peptide.
234. The method of claim 232, wherein the protein that is phosphoralated by AMPK is one of more proteins selected from the eNOS, nNOS and nNOS μ .
235. The method of any one of claims 229-234, wherein measuring the indicator of cellular AMPK activity further comprises measuring glucose uptake by cells and/or tissue.
236. The method of any one of claims 235, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
237. The method of any one of claims 235, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.
238. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises measuring the effect of the compound on glucose uptake glucose uptake by a cells and/or tissue.

239. The method of claim 238, wherein the cells and/or tissues are selected from:
myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
240. The method of claim 238, wherein the cells are selected from the group consisting of: 3T3-L1 cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.
241. A method for determining the degree to which a candidate compound activates Akt, the method comprising:
- 1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and
 - 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;
- wherein the candidate compound is a cytokinin having the structure:

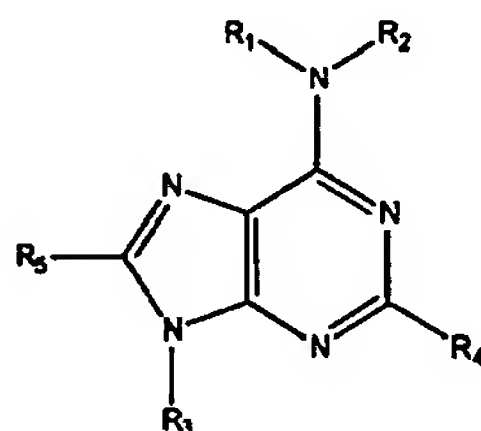


(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,
wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

242. The method of claim 241, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and

- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

243. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

- 1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine;

2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

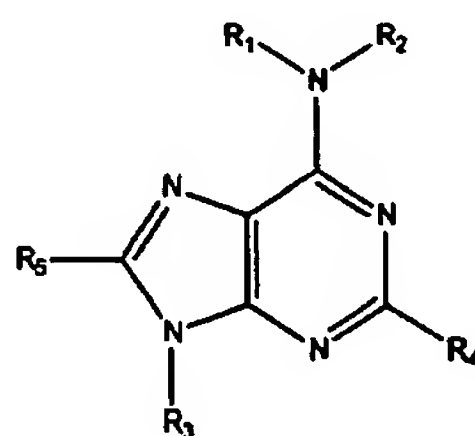
244. The method of claim 243, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-

glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

245. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

- 1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

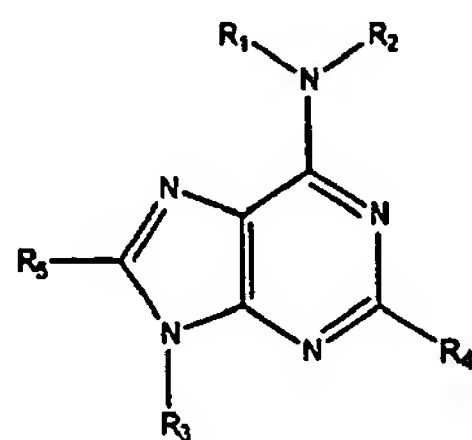
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

246. The method of claim 245, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

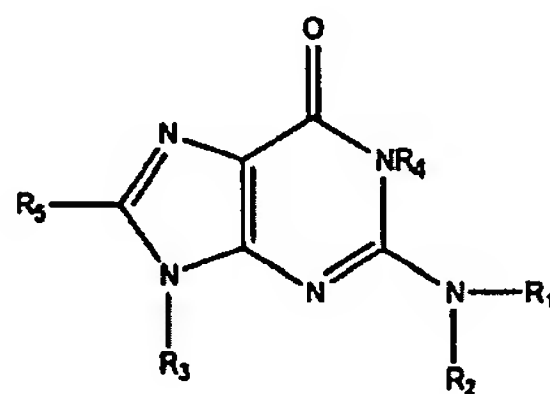
wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

247. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

- 1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

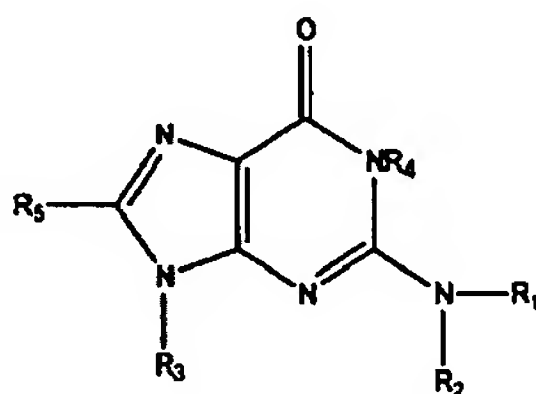
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;
wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and
wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

248. The method of claim 247, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

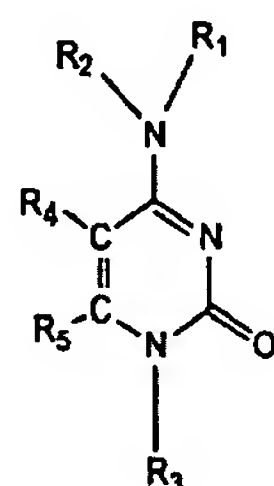
wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

249. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

- 1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

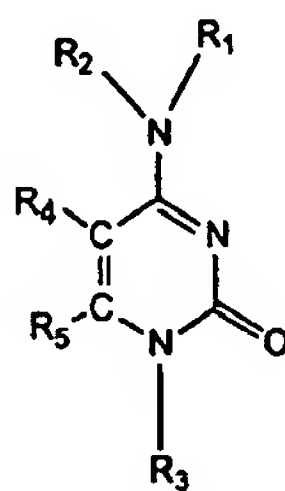
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

250. The method of claim 249, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

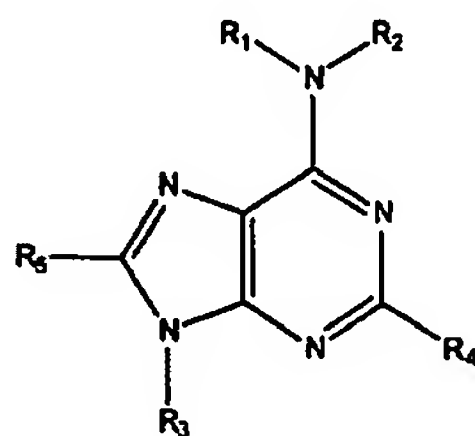
wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

251. The method of any one of claims 241-250, wherein measuring the indicator of cellular Akt activity comprises (i) measuring the phosphorylation of Akt and/or (ii) measuring the phosphorylation of a protein that is phosphorylated by Akt.
252. The method of claim 251, wherein measuring the indicator of cellular Akt activity comprises measuring the phosphorylation of Akt.
253. The method of claim 252, wherein measuring the phosphorylation of Akt comprises measuring the phosphorylation of the serine 473 residue of Akt.
254. The method of claim 251, wherein measuring the indicator of cellular Akt activity comprises measuring the phosphorylation of a protein that is phosphorylated by Akt.

255. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a cytokinin having the structure:



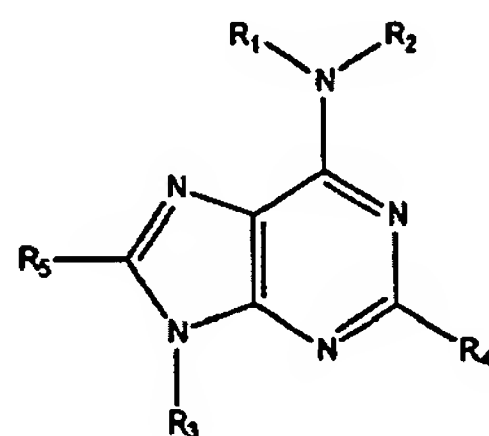
(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

256. The method of claim 255, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

257. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:
- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

- 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin

hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

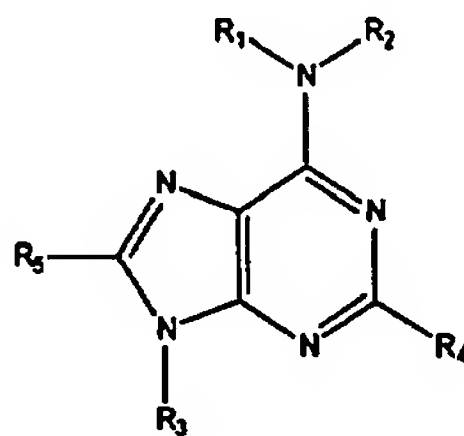
258. The method of claim 257, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7- β -D-glucoside; dihydrozeatin-9- β -D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-

isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

259. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

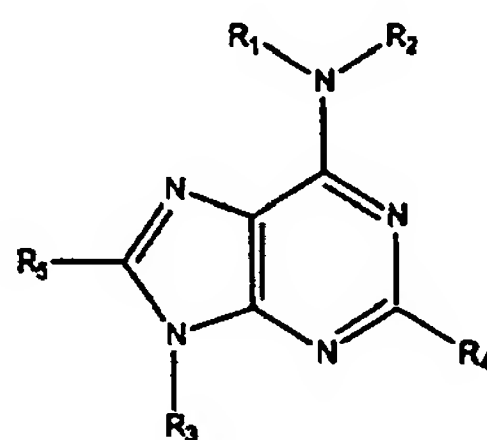
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

260. The method of claim 259, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

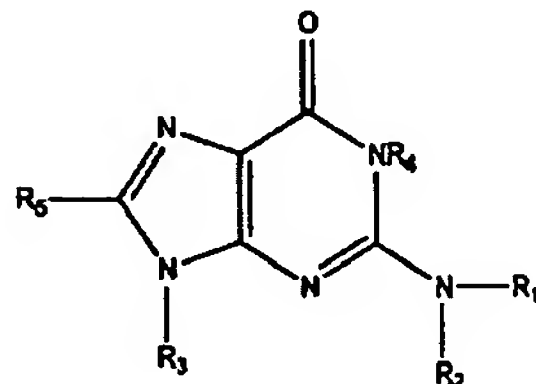
wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

261. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

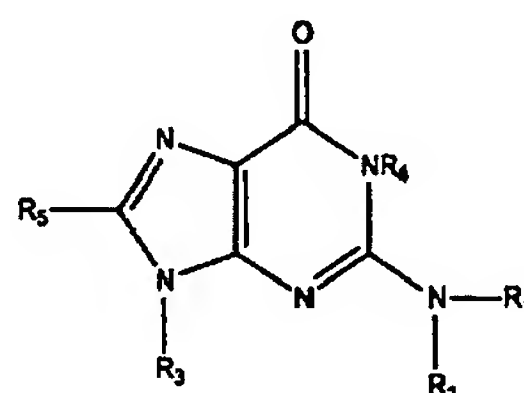
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

262. The method of claim 261, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

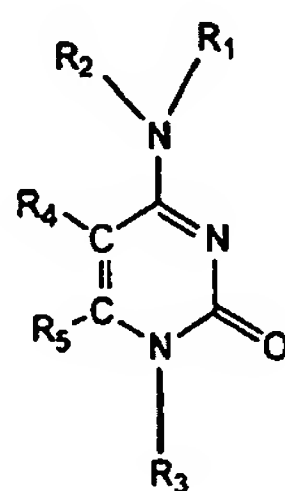
wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

263. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

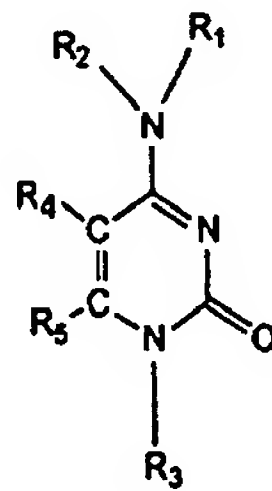
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not hydrogen; and

wherein at least one of R_1 , R_2 , R_4 , and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

264. The method of claim 263, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

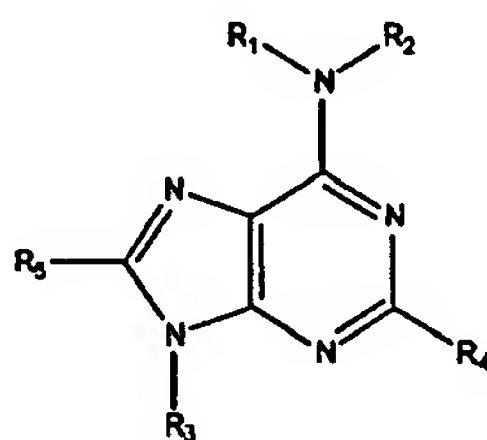
wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

265. The method of any one of claims 255-264, wherein measuring the indicator of Glut-4 content comprises (i) measuring Glut-4 content of the cells and/or tissue and/or (ii) measuring glucose uptake glucose uptake by the cells and/or tissue.
266. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring Glut-4 content of the cells and/or tissue.
267. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring total Glut-4 content of the cells and/or tissue.
268. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring glucose uptake glucose uptake by the cells and/or tissue.
269. The method of any one of claims 255-268, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
270. The method of any one of claims 255-268, wherein the cells are selected from the group consisting of: 3T3-L1 cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

271. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a cytokinin having the structure:



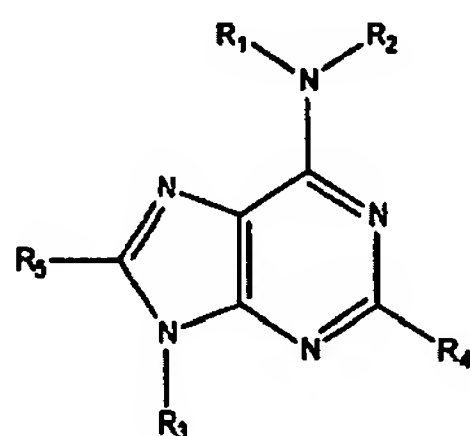
(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

272. The method of claim 271, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ is H or alkyl, lower alkyl, alkenyl, or acyl;
- R₂ is alkyl, lower alkyl or alkenyl;
- R₃ is hydrogen, alkyl, lower alkyl or saccharide; and
- R₄ and R₅ are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

273. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

- 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin;

trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

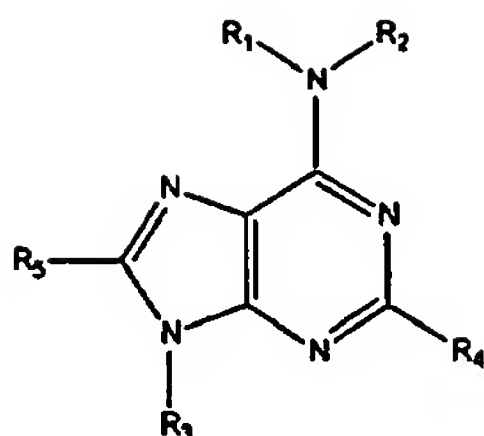
274. The method of claim 273, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-

isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

275. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,

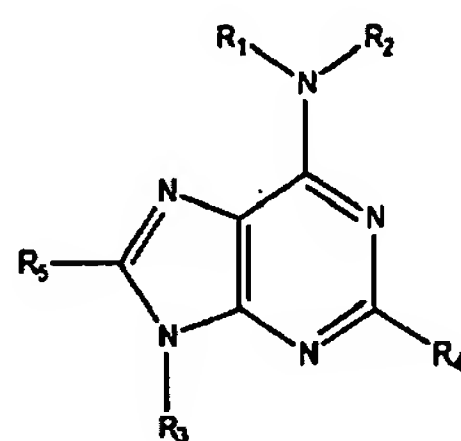
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

276. The method of claim 275, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph
and/or pharmaceutically acceptable salt thereof,
wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

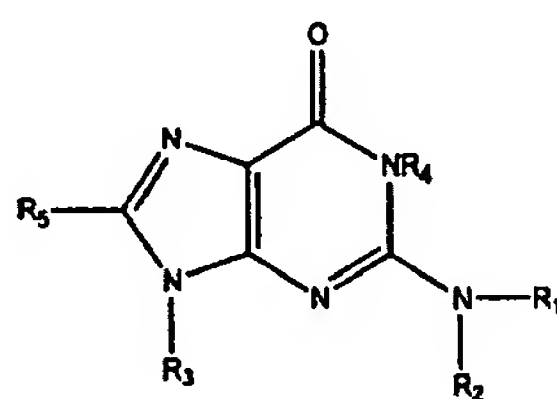
wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

277. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

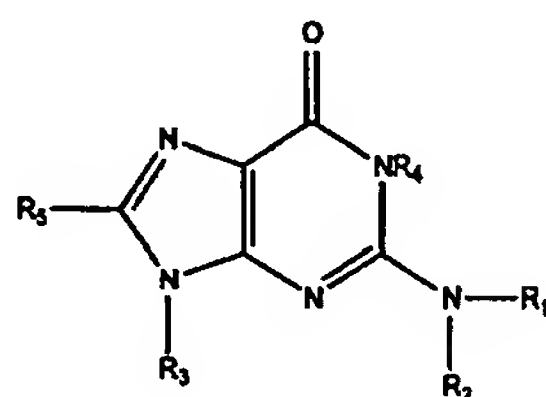
- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,

deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

278. The method of claim 277, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

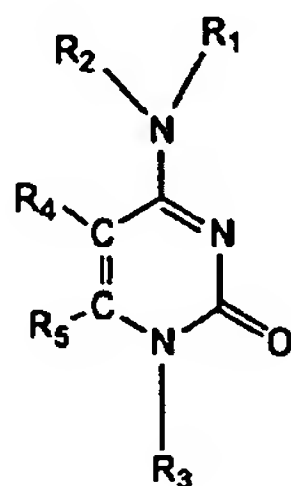
wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

279. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

- 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and
- 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

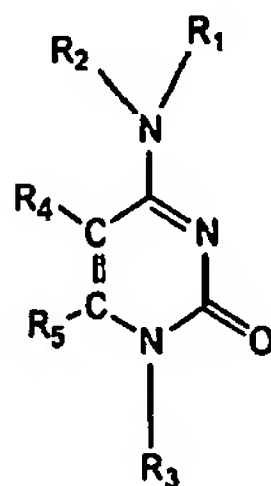
- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

280. The method of claim 279, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph

and/or pharmaceutically acceptable salt thereof,

wherein:

- R₁ and R₂ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R₃ is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide,; and
- R₄ and R₅ are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; and

wherein at least one of R₁, R₂, R₄, and R₅ is not hydrogen when R₃ is ribosyl,

deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

281. The method of any one of claims 271-280, wherein measuring the indicator of Glut-4 translocation in the cells and/or tissue comprises (i) measuring plasma membrane Glut-4 content of the cells and/or tissue and/or (ii) measuring glucose uptake glucose uptake by the cells and/or tissue.
282. The method of claim 281, wherein measuring the indicator of Glut-4 translocation in the cell comprises measuring plasma membrane Glut-4 content of the cells and/or tissue.
283. The method of claim 283, measuring the indicator of Glut-4 translocation in the cells and/or tissue comprises measuring glucose uptake glucose uptake by the cells and/or tissue.

284. The method of any one of claims 271-283, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.
285. The method of any one of claims 271-283, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

ABSTRACT

Compounds and compositions are disclosed that modulate one or more of various metabolic activities. Among the disclosed compounds and compositions are those that potently activate AMPK and/or Akt. The use of such activators, as well as compositions comprising such activators, to increase intracellular levels of activated AMPK and/or activated Akt to result in one of a number of beneficial effects in an organism is also disclosed. Compounds and compositions having blood glucose lowering activity and/or lipid lowering activity are disclosed as are related methods using them. An aspect of the present invention is particularly concerned with an anti-diabetic agent and with an anti-diabetic composition containing the anti-diabetic agent. Another aspect of the invention is particularly concerned with methods relating to treating insulin resistance and/or diabetes, including type II diabetes. Also disclosed are screening methods for screening purine derivatives and/or pyrimidine derivatives to identify compounds having an activity to modulate one or more of various metabolic activities and/or for use as an anti-diabetic agent. The disclosed screening methods include measuring the ability of a purine derivative and/or a pyrimidine derivative to increase intracellular levels of activated AMPK and/or activated Akt.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/025026

International filing date: 03 August 2004 (03.08.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/493,447
Filing date: 08 August 2003 (08.08.2003)

Date of receipt at the International Bureau: 23 September 2004 (23.09.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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